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NEWER KNOWLEDGE OF EPILEPSY*

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MORE has been learned about the real nature of epilepsy in the past 20 years than in the preceding 20 centuries. We have only two or three minutes for each year of these 20; therefore, I shall for the most part limit myself to the data which my associates and I have been able to collect.

ECONOMICS OF EPILEPSY

Before considering the science of epilepsy, let us think for a moment of its economics. When our world warring is ended, medicine like every other activity will need to link arms with economics. The amount of money spent in the prevention and treatment of various diseases must be related to the cost of these diseases and to the possibility of restoring their victims to productive activity. Epilepsy is a much larger and more costly problem, and also a more hopeful one, than most persons realize. Epileptics in the United States number something over half a million, as many as the victims of active tuberculosis, of diabetes or of infantile paralysis. The tenth part of these patients who are hospitalized at public expense occupy one-tenth as many hospital beds as all medical, surgical, and obstetrical patients combined. Epileptics, no matter how able-bodied or clear-minded, are denied service in our armed forces and in our industries. As soldiers are killed or brain wounded, both the relative and the absolute numbers of persons subject to convulsions will increase. Attempting to find the cause and cure of seizures is a handful of clinicians and research workers—members of the American Branch of the International League against Epilepsy. Helping to lighten public ignorance and prejudice are such organizations as the Harvard Epilepsy Commission and the Laymen's League against Epilepsy.[1] Their resources are grotesquely small. For purposes of medical research designed to meet the aggressions of epilepsy, this nation in the last two decades has probably not expended the price of a single bomber. Whether the meager thousands were profitably spent you should decide after hearing the résumé which follows.

* Read at the St. Paul meeting of the American College of Physicians May 4, 1942.

Fasting and Its Sequelae

Many a discovery has had a bizarre beginning. Twenty years ago an osteopathic practitioner announced that prolonged starvation had a restraining effect on convulsions. This statement was confirmed by Geyelin,[2] Talbot,[3] and others. The suggestion was early made that this auto-cannibalistic diet might be replaced by one which simulated starvation, a diet containing a plethora of fat and a minimal amount of carbohydrate and protein. This ketogenic diet proved as effective as fasting and far more practical. It is valuable in the treatment of children, especially those having frequent petit mal. Early investigators assumed that the diet was beneficial because of the sedative action of the ketone bodies. However, acidosis induced by other means, such as the administration of large quantities of hydrochloric acid or of acid forming salts, was found to inhibit seizures. For short periods petit mal seizures could be controlled by the inhalation of air rich in carbon dioxide or by the auto-manufacture of lactic acid by means of muscular exercise. Conversely, alkalosis induced by overventilation or by ingestion of large quantities of alkali tended to precipitate seizures. Like a touchdown made from the opening kickoff, it seemed as though these observations had won the game. Epilepsy is an alkalosis: acidify and all will be well. This hope, however, was quickly dissipated. Study demonstrated no abnormality in the acid-base balance of epileptics, but only that an acute upset of the patient's balance would alter the frequency of his attacks. Alkalosis precipitated seizures only in the epileptic. Furthermore, petit mal seizures were more easily influenced by chemical changes than grand mal, a circumstance which seemed to depend, as later study showed, on the peculiar electrical cortical activity associated with petit mal.

Continued investigation disclosed also, that disturbance of the acid-base balance is only one of various factors which may alter the frequency of seizures. In patients subject to petit mal these seizures could be induced by mild degrees of anoxemia and could be inhibited by increasing the oxygen tension in the patient's tissues. The latter condition was accomplished by having patients breathe pure oxygen while in a compression chamber under three atmospheres of pressure.[4] Temple Fay[5] helped his patients by dehydrating them, and McQuarrie[6] induced seizures by a large fluid intake combined with injection of pitressin. It was found that frequency of seizures could be altered also by changes in the concentration of blood sugar, blood calcium, and possibly also cholesterol and vitamins. Sudden and widespread anemia of the brain should be an effective precipitant of seizures, if old theories of vascular spasm are correct. However, when syncope was induced in 20 patients subject to grand mal, a convulsion was observed in only one. Of more importance, the volume of blood passing through the brain was not decreased immediately before the occurrence of spontaneous seizures.[7]

In this period of search, eager investigators hoped that anoxemia, anemia, hydration, or hypoglycemia was the fundamental cause of epilepsy. Like alkalosis, however, these various conditions were not primary causes but only precipitating factors. They were not the inner mechanism of seizures but the threshold. In the analogy of the overflowing reservoir, they were not the impounded waters, but the restraining dam. Statements should not be too categorical. The secret of epilepsy lies in the chemistry of the discharging neurones of the brain. The relationship of neuronal and of bodily chemistry has yet to be clarified. The amazingly low oxygen tension of the brain recently announced by Bronk [8] is illustrative. Another example is the action of anticonvulsant drugs. Bromides and phenobarbital are sedatives, whose soothing influence is useful in many conditions, and apparently of value in epilepsy only because they increase the seizure threshold. On the other hand, the drug whose worth was proved by our colleagues Merritt and Putnam [9] has little hypnotic effect, seems to have value only in epilepsy, and in some instances at least not only stops seizures, but composes the underlying disordered electrical potentials of the brain. I refer to sodium diphenyl hydantoinate (dilantin sodium, or, officially, phenytoin sodium), the drug of choice in epilepsy. That this drug is relatively ineffective for petit mal, a type of seizure so readily affected by changes in pH, in carbon dioxide tension, and in the glucose content of the blood, points the need and the opportunity for further research.

Having uncovered the valuable facts which have been mentioned, laboratory workers were at a loss for an approach to the core of the problem, the cause or causes of seizures. Beginning with Hippocrates, clinicians have advanced many different groups of causes. At present, four principal ones are recognized. In inverse order of importance, these are: emotional, somatic, pathologic brain lesions, and heredity. For the purpose of ascertaining the importance of these factors, records were analyzed of some 2,000 patients examined by coöperating neurologists throughout the country. Of these clinic and private patients, approximately three-fourths gave no history or, on examination, no evidence of brain injury or of a physical or emotional disturbance which could be considered the primary cause of seizures. In the remaining 25 per cent of patients, the cause in practically all was assigned to some lesion of the brain.

Is the preponderant "unknown" area of epilepsy synonymous with heredity? Are lesions of the brain alone sufficient to explain seizures? These questions bring us to the old contested area of "essential" versus "symptomatic," which overlies the still more ancient battleground of "heredity" versus "environment." Hippocrates placed himself on the side of heredity. Through the centuries words have been hurled back and forth with vigor but only rarely have they been edged with facts. The electroencephalograph is a new and potent weapon, a rifle come to the aid of bows and arrows.

Electrical Pulsations of the Brain

A few years ago research in epilepsy had reached a blind alley. The secrets of the human brain, hidden behind the bony wall of the skull, seemed inscrutable. Then two discoveries breached this wall. First Myerson, Halloran and Hirsch,[10] psychiatrists of Boston, found that a needle could safely be inserted into the lumen of an internal jugular vein. Blood withdrawn in this manner provided a means of studying the metabolism of a patient's brain. Second, Berger,[11] a psychiatrist in Germany, demonstrated the feasibility of recording electrical pulsations of the cortex which were transmitted through the skull. Research of the last few years has been based on these two technics.

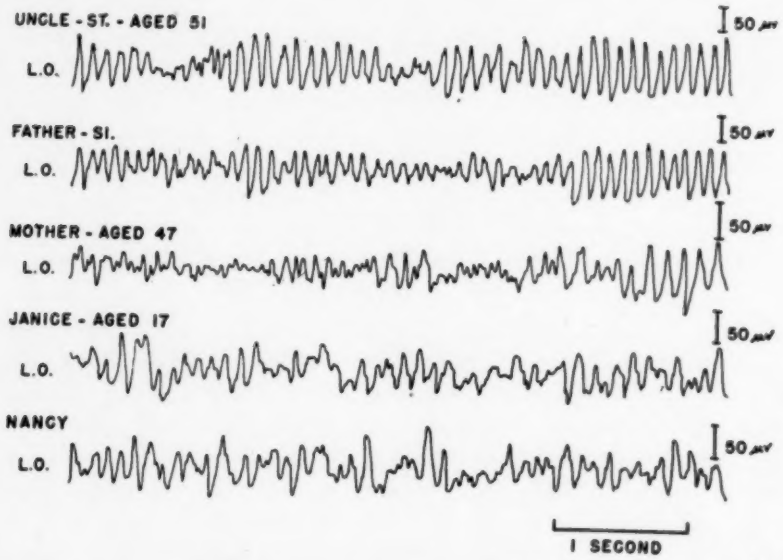

Fig. 1. The electrocardiographic records of identical twins, aged 51, the wife of one, and the twin daughters of this union. All are without personal or family history of seizures, yet the records of the mother and the twin daughters are irregular in frequency and voltage. The signal at the right of each tracing indicates microvolts, and the horizontal line at the bottom marks one second.

The subject of electroencephalography as it applies to the problem of epilepsy can be dealt with only in headline fashion. Pronounced disturbances in the pulsations of the electrical waves of the brain are present in all patients during epileptic seizures and in about 90 per cent of patients in a seizure-free period. The three main types of seizures are characterized by different types of dysrhythmia. Interparoxysmal seizure discharges, although usually widely dispersed over the cortex, may in certain patients be confined to a certain discharging area. Epilepsy may be called a cerebral dysrhythmia. The adjective "a" requires emphasis because disordered patterns of brain waves are not confined to persons who are subject to seizures, but are present

in an undue proportion of individuals whose conduct or whose psychical processes are abnormal: behavior problem children, "psychopathic personality" adults, alcoholics, and inmates of prisons. Dysrhythmia is also present in a small proportion of persons who by all ordinary standards are normal.[12]

Thus electroencephalography has proved of the greatest use in the understanding and the diagnosis of epilepsy, in the localization of cortical lesions, and to a smaller extent in judging the success of treatment. Recently an even wider field of potential usefulness has appeared. In spite of the fluid-like characteristics of brain waves and their alterability by changes in brain activity or brain chemistry, the pattern of the waves under standard conditions has individuality. In fact, this pattern seems to be a hereditary trait. The evidence for this bold statement lies in a study of the brain waves of twins. In the early days of this technic Davis and Davis [13] examined nine identical twins and found that the wave patterns of twins were alike. Recently Dr. and Mrs. Gibbs and I have made records of 77 twins, similar or dissimilar, normal or epileptic. In general the brain waves of similar twins who have not suffered brain injury are indistinguishable, whereas the waves of dissimilar twins are unlike. This statement is based on a study of 56 twins (44 monozygotic and 12 dizygotic) who were not subject to seizures or had not suffered brain injury. The "normal" monozygotic twins included 15 whose records were classed as abnormal. Mrs. Gibbs, who interpreted the records, was asked to decide which records were or were not identical. In 86 per cent of the cases her judgment coincided with the clinical evidence of identity, in 11 per cent she was doubtful, and in 5 per cent she was wrong. This 86 per cent represents a high correlation for such a fluid trait. The brain waves of twins of two generations are shown in the accompanying figure. The twin girls have similar but abnormal brain waves. The record of the mother is also abnormal, whereas those of the father and his twin brother are similar and normal. The dysrhythmia of the daughters, therefore, came from the mother.

If the brain wave pattern is an hereditary trait, it should be possible to trace the heredity of conditions which are associated with disordered brain rhythms, and to determine persons who are "carriers" of the disorder, and incidentally to settle the old question of heredity versus environment in the etiology of epilepsy. With this end in mind, electroencephalographic tracings have been made of 312 members of the epileptics' immediate family. Fifty-two per cent of these tracings were classed as definitely abnormal, 11 per cent as doubtful, and 37 per cent as normal. Thus the incidence of dysrhythmia either in the general population or among the patient's near relatives is at least 20 times the incidence of epilepsy in the general population or among the relatives of patients. Even more significant from the standpoint of genetics are the results obtained when both parents of patients were tested. This has been done for 88 families. In 27 per cent both parents had definite dysrhythmia, which is 27 times the expected number if one person in 10 is

dysrhythmic. In only 9 per cent of the families were the records of both parents clearly normal.

Returning to the subject of twins, study was made of 19 twins, in whom one or both members were subject to seizures. Of this group, there were six identical twins, neither of whom had a history suggestive of brain injury and both of whom had dysrhythmia. In three cases both of the twin members had seizures, and in three cases the unaffected member has had a seizure after the original electrical records were made. There were also six identical twins of whom only one co-twin had had a seizure. Because the co-twins have the same heredity, either heredity is of no account in the affected twin, or his seizures must be due entirely to environmental causes. This is the alternative usually discussed, but the electrical studies indicate that neither is correct. In five of these identical twins, only one of whom has chronic epilepsy, the normal co-twin's electrical record was, like the patient's, abnormal. In each instance the patient had suffered brain injury. The sixth twin furnished an example of what might be called temporary symptomatic epilepsy. One of identical twin girls had a few convulsions and dysrhythmia following a cerebral concussion. Several months later seizures had not recurred, and brain waves had become normal and indistinguishable from those of her twin sister.

These electrical studies lead to the conclusion that manifest epilepsy is not inherited but that a predisposition or susceptibility is inherited. A similar statement might be made about diabetes, obesity, hypertension and many other disorders. The unique feature about epilepsy is the suggestion that the predisposition may in most instances be disclosed by electrical tracings, and these laboratory recordings may be of great value to the physician, to the patient and to society when decision must be made with reference to marriage and procreation.

The facts here presented must be viewed against the background of other facts, namely that except for the three a second alternate dart and dome formation of petit mal, the dysrhythmia of epilepsy is not peculiar to it. Dysrhythmia may accompany paroxysmal disorders of conduct, or of thought, or for all we know, may accompany genius or high achievement. Eugenics, prolific in promises, has proved sterile in practice because eugenic measures, to be effective in a reasonable number of centuries, must be applied not only to the victims of a disorder but to the much larger numbers of healthy "carriers." If persons with pronounced dysrhythmia are the healthy "carriers" of epilepsy and allied disorders, including, perhaps, genius, then electroencephalography is a technic capable of improving the race and undoing some of the eugenic ravages of war.

Chemical Etiology of Epilepsy

Persistent search for the answer to certain problems results in discovery of the answers, but often these answers lead only to problems far more dif-

ficult. Puzzles which intrigued the investigators of epilepsy several decades ago—allergy, gastrointestinal functions, metabolism of the body as determined by analysis of the urine, spinal fluid, or of blood drawn from an arm vein—have been answered in the negative and now seem naïve and futile. Search for the answer to epilepsy has led to the brain, and past all dead or foreign tissues of the brain to its functioning, discharging cells. Investigators must now accomplish the impossible and peer within these and other cells.

Behind the neurones of the brain lie the germinal tissues. Germ cells, we are told, are packed with genes, each gene presumably a large protein molecule. The particular germ cell which is antecedent to the epileptic contains a gene or genes which when transferred to the neurones of the brain give these cells a peculiar chemical composition or reaction, which in turn disturbs their normal rhythmic discharge. The same germ cell may or may not contain another gene which results in disturbance of the normal rhythm of the autonomic nervous system (migraine) or a gene which represents mental deterioration, or a gene which produces various physical dyssymmetries.

The disturbances in the pulsations of discharging clusters of neurones can be registered by the electroencephalograph. The chances are many to one that these peculiar pulsations will not be accompanied by any unusual behavior of the individual. He has asymptomatic dysrhythmia, a condition which was unknown and unsuspected until the recent arrival of prying medical scientists. In a minority of dysrhythmic individuals, however, because of injury or other environmental influences, the unusual electrical pulsations become externalized and accompany unusual patterns of thought or of physical behavior. When paroxysmal, these unusual actions have been called grand mal, petit mal, or psychic seizures. Doubtless there are other conditions not ordinarily called epilepsy, characterized by periods of unsocial behavior, which physiologically are allied to epilepsy and should be treated as problems for the doctor and the chemist and not primarily problems for the preacher or the prison.

There is another type of epilepsy which is not based on a constitutional defect of discharging cells, but arises through the injury or the disturbance of cells which were normal. Such injuries whether mechanical or chemical may give rise to dysrythmia, which may be short-lived and asymptomatic, or may gradually increase and spread until seizures result. This is the condition, probably rare, of symptomatic epilepsy.

Dramatic are the advances achieved through use of Berger's discovery, but behind the peculiar electrical pulsations of the brain lies the unknown chemistry of discharging nerve cells. At this point a study of the blood as it passes through the brains of patients, and as it influences the electrical pulsations of the brain, is crucial. Studies made possible by the technic of Myerson, Halloran and Hirsch [10] have shown that in normal subjects the respiratory quotient of the brain is unity and the metabolism of the brain is closely dependent on that of glucose. The arterial and internal jugular

blood contains a lower concentration of carbon dioxide in petit mal patients than in normal persons. Also in these patients the respiratory quotient of the brain is below unity and the brain burns less glucose per unit of oxygen than it should.

These chemical-electrical studies have demonstrated the relatively large importance of carbon dioxide in the activity of the brain. Small changes in carbon dioxide tension are of far greater importance than small changes in the tension of oxygen. In states of anoxemia sufficient to produce unconsciousness and dysrhythmia the addition of carbon dioxide will restore consciousness and a normal rhythm. In addition to increasing the oxygen saturation of arterial blood, and its oxygen dissociation curve, carbon dioxide has a specific effect in altering the cerebral circulation so that fluctuations in the carbon dioxide tension of the brain are minimized. Studies of brain metabolism in relation to the successful treatment of dysrhythmia in the individual seem not incapable of solution. Great is the gain scored by phenytoin sodium. There is no reason why other, and even more effective, drugs should not be found.

The term heredity has a fatalistic connotation. Two facts mitigate hereditary influence in relation to epilepsy. First, the indicator of heredity, dysrhythmia, is not in itself enough to produce epilepsy. Some insult to the brain in the form of physical injury or physiological upset is also required and may possibly be avoided. Second, dysrhythmia itself is a fluid characteristic and may possibly be modified by chemical means.

Truly gains against epilepsy in the past 20 years have been great, but more conclusive action is possible, if funds and gifted searchers address themselves to the task. This task is 20 times greater, 20 times more important than the control of seizures. Physician scientists must learn to control the disturbed brain waves of persons who carry a predisposition to epilepsy or to some disorder physiologically allied to it.

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THE FRAUDULENT USE OF DIGITALIS TO SIMULATE HEART DISEASE *

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During the summer of 1937, nationwide attention was attracted by reports in professional publications and in the lay press of an extensive criminal racket based on attempts to obtain payments on disability insurance by feigning heart disease. The writer was detailed as medical advisor to the U. S. District Attorney in New York City, and in that capacity obtained information upon which this report is based.[1]

The malefactions here described came under the jurisdiction of the Federal Government because they involved the use of the United States mail to defraud. Official inquiries were first conducted by postal inspectors. When sufficient evidence was obtained, the investigation was conducted by the U. S. District Attorney. A number of persons were arrested, arraigned, tried, and convicted. Others were questioned. Where it was evident that State laws had been violated, many of the defendants were subsequently tried before State courts.

Method of Operating

This scheme for acquiring money through deceit had its inception during the economic depression, about 1931. Although conducted in the main by two firms of lawyers, it involved physicians, "runners," policyholders, and even employees of life insurance companies. Many innocent persons, especially physicians, were embarrassed and even subjected to grand jury investigations.

During the period before the depression life insurance companies ventured into the field of health insurance to the extent of making available at reasonable rates insurance against total and permanent disability. The amount of insurance obtainable was dependent on the size of the policy. Most companies provided 10 dollars per month coverage for each thousand dollars of life insurance.

The conspirators operated by inducing policyholders of life insurance with total and permanent disability features to make fraudulent claims for disability payment. Policyholders were first approached by lawyers' "runners," or agents who persuaded them to take advantage of the disability clauses in their insurance policies by claiming disability. Often these "runners" were apprised that the policyholders, who were for the most part small business men, were in financial difficulties because of the depression. The "runners"

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then introduced them to the lawyers who agreed to take their cases on a percentage basis.

Inquiries were then made concerning disabilities. In most instances the claimant did not have a sufficient disability to cause him to be totally and, presumably, permanently disabled. In that event it would be necessary to invent a spurious disabling disease or to exaggerate a nondisabling condition. Other claimants were the kind of psychoneurotic individuals who resort to litigation on the slightest pretense. In addition, unfortunate persons with conditions sufficient to justify claims for disability fell into the hands of these conspirators, and were put to the expense of paying exorbitant fees which could have been avoided. Sometimes they were induced to withhold claims for disability until they obtained additional insurance through misrepresentation. The lawyers even went so far as to pay the premiums.

Heart disease was frequently used as a claim for disability insurance because it is easy to simulate and difficult to disprove, and because jurors are likely to give the claimant the benefit of any reasonable doubt. After the policyholder had become a client, the next step was to "build up" a clinical picture of heart disease, especially coronary arteriosclerosis with angina pectoris, frequently associated with a spurious attack of coronary occlusion.

The claimant was first coached in the symptoms of coronary insufficiency. In this, the services of physicians were employed, although later the lawyers, with the help of medical textbooks, acquired a working knowledge of these conditions which enabled them to do their own tutoring. The claimant was next induced to visit his family physician with complaints indicating coronary arteriosclerotic heart disease. In most instances the family physician was innocent of unprofessional conduct. The claimant would often give a history suggesting a previous coronary occlusion, taking care that this episode was alleged to occur while away on vacation or under other circumstances in which it was impossible for the family physician to be present.

The next step was to develop evidence which could be used in court. The claimant not infrequently visited several general practitioners. Sometimes he feigned heart disease in a public place, and was often rushed to a hospital. Sometimes he went to a hospital for the treatment of bona fide conditions, and even underwent operations. Here, notations concerning heart disease were made on the records, consultations held, and attacks feigned.

As a final measure to convince the life insurance company or to assure success in event of litigation, an effort would be made to obtain from a reputable cardiologist a consultation report favorable to the claim. The claimant would be sent to the cardiologist by his family physician or by a physician working with the conspirators. The claimant would be coached in the symptoms of heart disease. Frequently, digitalis or some of its derivatives would be administered either to produce an arrhythmia or to produce effects on the electrocardiogram simulating coronary disease. Claimants were often directed to run to the office of the consultant, climb stairs,

drink several cups of coffee, or even go on a debauch. Most of the cardiologists were only guilty of credulity, a shortcoming characteristic of the homo Americana. If his report was favorable, it was subsequently utilized; otherwise, it was consigned to the waste paper basket and another consultation obtained. It is interesting to note that consultations were postponed in order to give the digitalis time to take effect.

Meanwhile, the claimants were instructed to avoid business and remain at home. When sufficient "evidence" had been accumulated, the claims were submitted to the insurance companies for payment of total and permanent disability. On physical examination by physicians of the insurance companies or by qualified consultants, few objective clinical manifestations of organic heart disease would be uncovered. Despite this, the claims were paid at first without much protest because of the well-narrated history and the impressive array of medical testimony. It is extremely difficult to refute a plausible story of heart disease in a middle-aged person, especially in the presence of elevated blood pressure, other signs of arteriosclerosis, diabetes mellitus, or other degenerative diseases. The tendency is to give the claimant the benefit of any reasonable doubt, knowing that juries generally take a similar view.

After a while the conspirators became less careful in the selection of clients. Persons not only in the fifties but also in the forties and even thirties were making claims for disability from heart disease. Although coronary occlusion is by no means rare in persons under age 40, the occurrence of a great number of cases naturally excites suspicion. Well-satisfied claimants not infrequently became "runners" for the lawyers, obtaining fresh business on a percentage basis. The "runners" for the two firms conducted a trade war, each offering better services at cheaper rates, thus disproving the adage that there is honor among thieves. Also, some claimants attempted to pyramid their gains by obtaining insurance from other companies under assumed names.

The claims were invariably handled by the attorneys on a percentage basis. Because of the danger that the claimant might become dissatisfied, talk too much, indulge in physical exercise, return to work, or the depression might end, the attorneys would endeavor to make a cash settlement. This was advantageous to the insurance company which could not foresee how long it would have to continue payments. To the claimant it was frequently disastrous, as he would surrender his life insurance as well as his disability insurance for a relatively small amount, much of which would be used to defray legal expenses.

In a typical case, a person with $25,000 life insurance with a disability clause providing for the payment of $250 a month for total and permanent disability would submit a claim for alleged coronary occlusion. It would take about six months to begin payments. The claimant would then receive a check for $1,500, most of which would go to the lawyers for services rendered. He would then begin receiving $250 a month, of which about a

fourth went to the lawyers. A cash settlement would then be made for perhaps $6,000. The lawyers would get $2,000 of this, and the claimant would surrender his entire life insurance policy for $4,000.

Extent of Conspiracies

Altogether, 84 persons were actively involved. Of these, six were convicted after trial, 38 pleaded guilty, 16 were indicted but pleaded not guilty, 20 confessed but were not indicted, and two were arrested but not indicted. In addition, there were 155 others against whom there was evidence of guilt but who have not been arrested, or indicted, or have not confessed.

Two physicians were convicted after trial, seven pleaded guilty and were sentenced, three were indicted but pleaded not guilty, 10 confessed but were not indicted, while among 11 others there was evidence of guilt at hand but they were not arrested, indicted, or convicted. Many other physicians unwittingly certified claimants as having heart disease, and were occasioned embarrassment and loss of time.

Life insurance policies amounting to more than 10 million dollars in more than 40 different life insurance companies were involved. Actual payments and cash settlements amounting to several hundred thousand dollars were made. The most important feature of this conspiracy was that as a result of this and other fraudulent practices, the cost of disability insurance has greatly increased, and most insurance companies have ceased issuing this form of insurance. This vitally affects many honest citizens who might otherwise receive this protection.

Use of Digitalis

Digitalis was administered in many cases to produce abnormal electrocardiograms which could be interpreted as due to coronary arteriosclerosis. Although the amount of digitalis given could not be determined with any great degree of accuracy, it appeared that in most cases it was given in comparatively small doses of about 0.1 gram three times a day. In most instances only a flattening of the ST intervals was produced; in others, varying degrees of auriculoventricular block occurred. Premature contractions were infrequently encountered. In the cases in which there were quite marked effects, either the dosage was larger than alleged or individual susceptibility occurred. The most frequent effect of digitalis on the electrocardiogram was to produce a pulling down of the ST segment rather than an actual inversion of a T-wave. In some instances the deeply depressed ST segment simulated a T-wave inversion. In a few instances actual T-wave inversions occurred.

Case Reports

Case 1. White male, aged 45 years, alleged heart attacks simulating coronary occlusion on October 14 and 25, 1933. He subsequently claimed angina of effort, and symptoms of congestive failure such as dyspnea even at rest, severe orthopnea, and

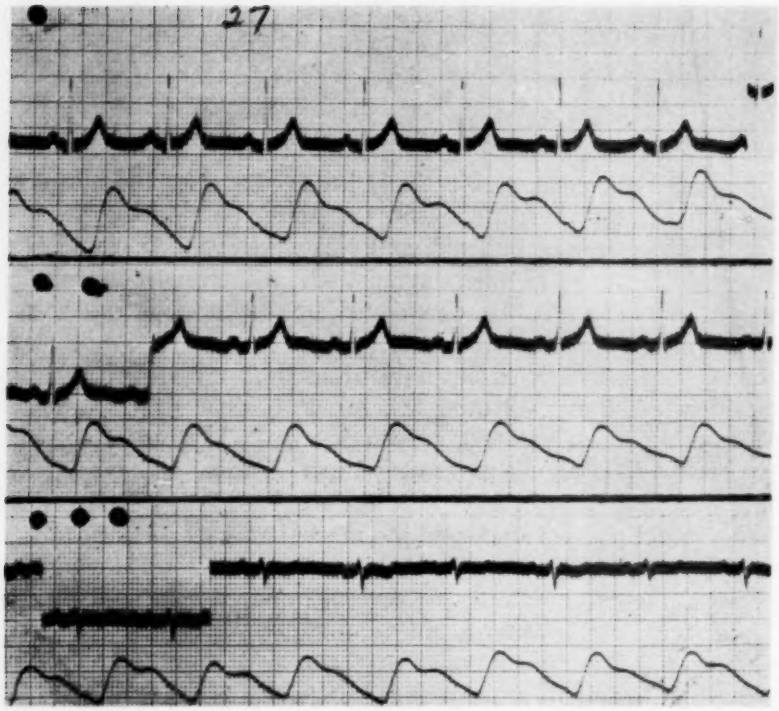

FIG. 1. *Case 1.* Normal electrocardiogram taken by physician representing an insurance company.

edema of the lower extremities. Other symptoms included Dietl's crisis and intermittent claudication. Figure 1 is a normal electrocardiogram taken on March 20, 1934, by a physician representing an insurance company. Figure 2 is an electrocardiogram obtained in a hospital on May 26, 1934, after digitalis was administered. It shows a true inversion of the T-wave in Lead III, notching and slurring of the QRS

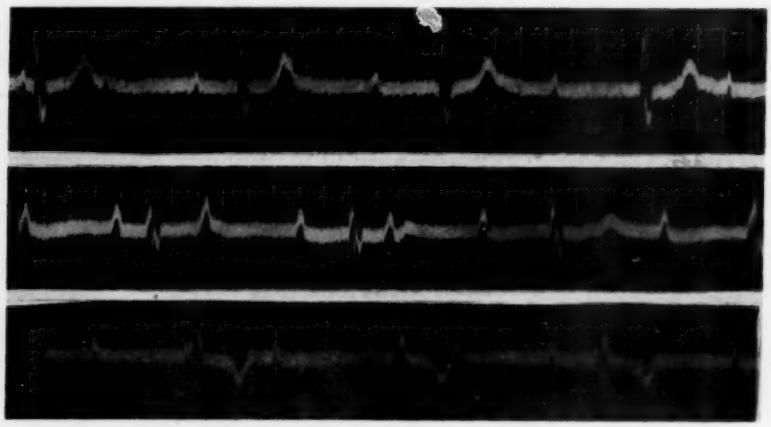

FIG. 2. *Case 1.* Taken in a hospital after digitalis was administered.

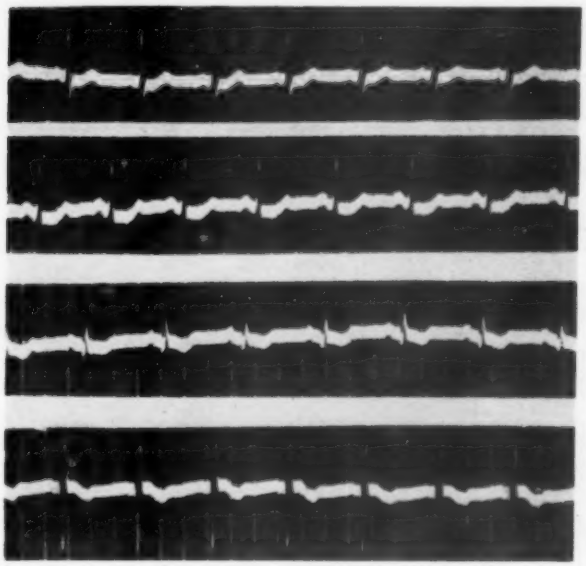

FIG. 3. *Case 2.* Taken after discharge from hospital but postdated to appear as though taken in hospital—shows digitalis effect.

complexes in all three leads and complete auriculoventricular dissociation. During a subsequent hospital admission, digitalis was administered surreptitiously with much less effect. Another tracing showed depression of the ST interval in Leads II and III, bradycardia, and inversion of Lead III.

He was admitted to hospitals on four occasions, three of which were spurious admissions to build up the case. The other admission was for appendicitis. On this

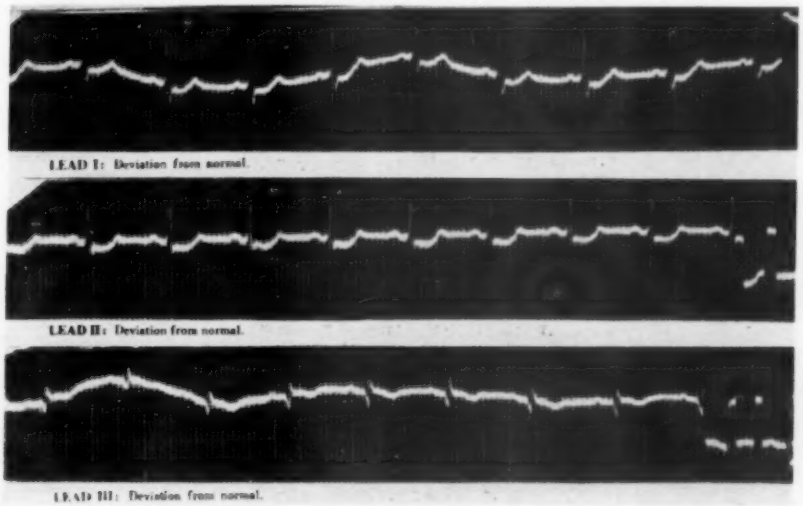

FIG. 4. *Case 2.* Considered indicative of myocardial damage "since digitalis administration has been denied."

occasion the claimant nearly lost his life on the operating table as a result of having one of the physicians in the ring perform the operation. Nevertheless, reference to previous attacks of angina pectoris was added to the records. This claimant also became a "runner" or agent for the attorneys. He subsequently confessed, turned government's evidence, and might have escaped with a suspended sentence had he not literally battered his way into jail for obstructing justice by furnishing information to the defense.

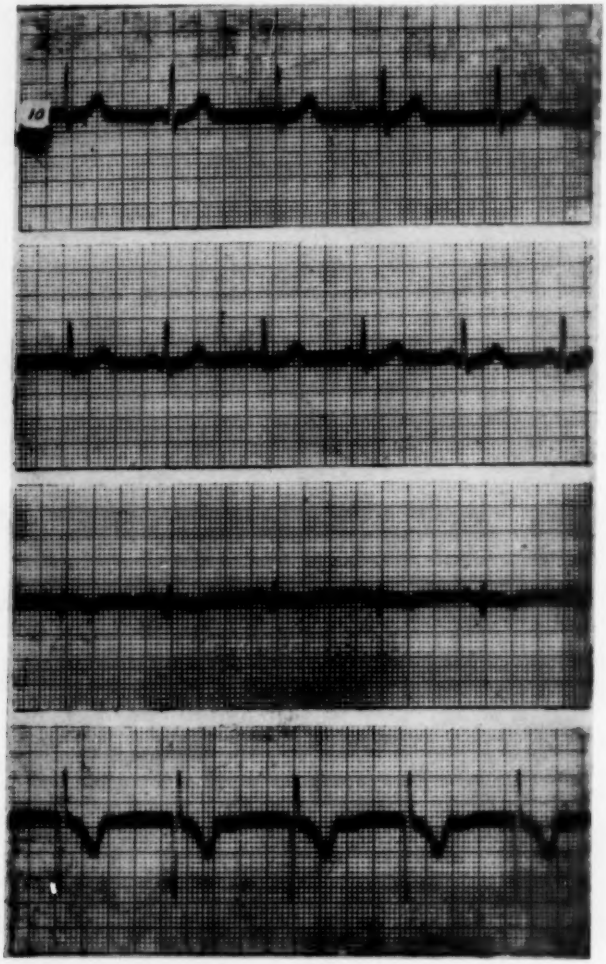

FIG. 5. *Case 2.* Normal electrocardiogram obtained after confession.

Case 2. White male, aged 38, claimed angina pectoris and progressive dyspnea beginning in October 1934. In December, he was admitted to a hospital by physicians who were subsequently convicted of participating in this fraud. A tracing, which was taken during this admission, showed depressed ST intervals in Leads I and II, and probably in Lead III, with a diphasic T-wave in Lead III. These findings were regarded as indicative of myocardial damage. He was readmitted to the same hospital by these physicians in July 1935, for a minor automobile accident. No electro-

cardiograms were obtained during this admission. A month later, however, tracings were obtained and postdated to make it appear that they were taken when the claimant was in the hospital. This was proved in court, proof being based on similar tracings seized in one of the defending physicians' offices. This electrocardiogram (figure 3) was interpreted as indicative of myocardial damage. Another tracing, which was taken at the office of a life insurance company, also shows depression of the ST

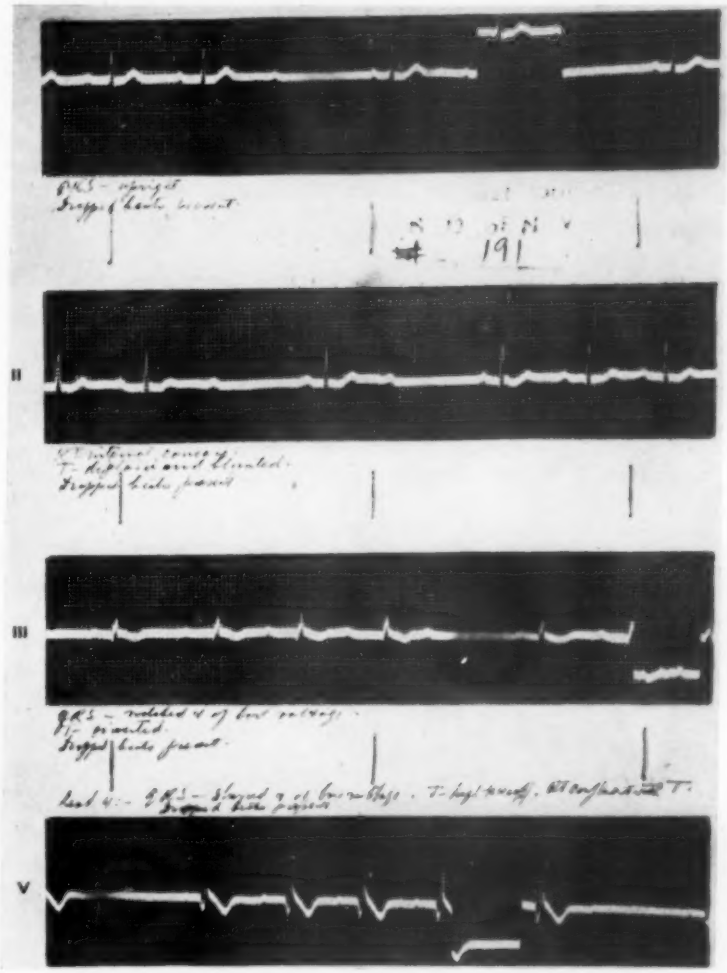

FIG. 6. *Case 3.* Abnormal electrocardiogram taken in a hospital after digitalis was administered.

intervals. It was interpreted as showing evidence of myocardial disease, and the claimant was considered disabled. A slightly greater digitalis effect is noted in a later tracing. Here, the consultant for the insurance company was so suspicious that he telephoned the referring physician and was assured that the claimant had not received digitalis. Still skeptical, he concluded his report, "If the patient is not taking digitalis, I would say that he is totally disabled."

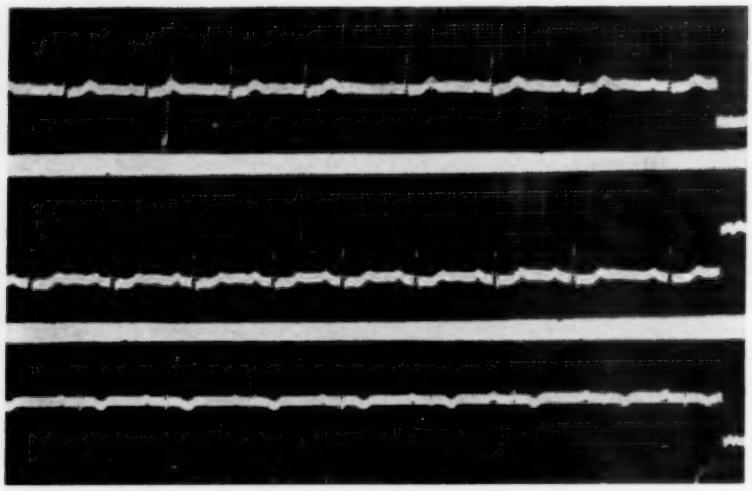

FIG. 7. *Case 3.* Taken by representative of insurance company who regarded myocardial damage as slight—indicative of minor digitalis effects.

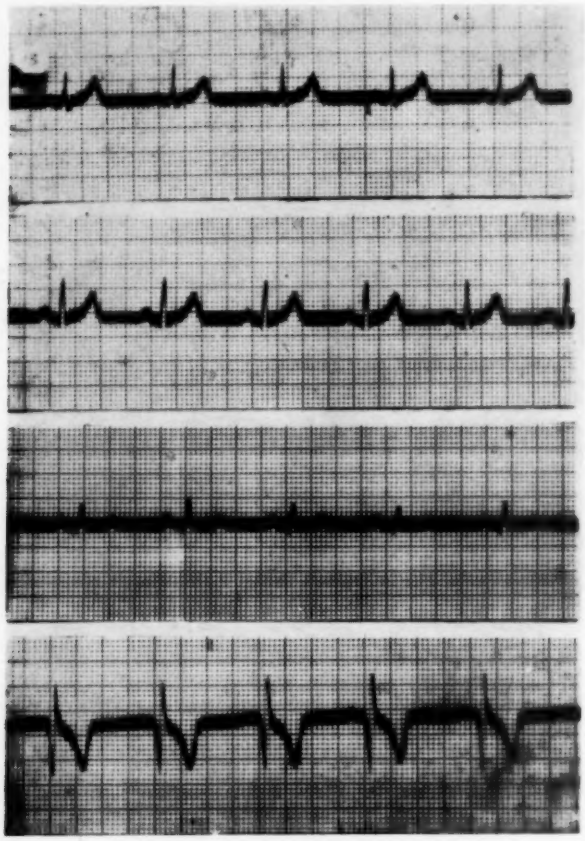

FIG. 8. *Case 3.* Normal electrocardiogram obtained after confession.

In figure 4, the ST intervals in Leads I and II are depressed, the T-wave in Lead II appears to be diphasic owing to the depression of the ST segment, and the T-wave in Lead III appears inverted for the same reason. There is also a rather deep Q-wave in Lead III. These findings were interpreted by a physician in the home office of a life insurance company: "It is conceivable that digitalis may cause the changes noted in the conventional and precordial leads, but highly unlikely. Since digitalis administration has been denied, it must be assumed that this record is associated with myocardial damage of coronary origin."

This claimant subsequently confessed participation in this fraud, and a physician admitted having given him digitalis and having coached him in the symptoms of heart disease. Figure 5, a normal electrocardiogram, was obtained after the claimant had confessed and was awaiting trial. He had not received digitalis for months.

Case 3. White male, aged 42, claimed total disability because of attacks of substernal pain stated to have begun while working in a grocery store in September 1936. He was hospitalized for heart disease in December 1936. During this admission an electrocardiogram (figure 6) was taken. This electrocardiogram shows a partial auriculoventricular block, depressed ST segments in Leads II, III, and the chest lead, and the appearance of inverted T-waves in Lead III and the chest lead, and a diphasic T-wave in Lead II, all due to a pulling down of the ST segments. A diagnosis was made of myocardial damage and dropped beats. The physician subsequently admitted surreptitious digitalization. Figure 7 was taken by a physician representing an insurance company. In his opinion the area of myocardial infarction was small, if existent. The depressions of the ST interval suggest a digitalis effect. Electrocardiogram (figure 8), which was obtained after confession, is entirely normal.

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RECOGNITION OF INCIPIENT THROMBOANGIITIS OBLITERANS IN YOUNG DRAFTEES *

By William E. Jahsman, M.D., F.A.C.P., and Robert H. Durham, M.D., F.A.C.P., with technical assistance of Nicholas P. Dallis, M.D.,
Detroit, Michigan

Few people would question the loyalty and patriotism of the average American. In recent months, however, all of us in the medical profession have seen the occasional young man of the draft age who described symptoms of peripheral vascular disease, just as others talk about trouble with the heart, the lungs, or the gastrointestinal tract, apparently in the hope that he might thus evade military service. When such suggestive peripheral blood vessel symptoms are described, we, as examining physicians, should remember that thromboangiitis obliterans can and does occur in young men, and make every effort to rule this disease in or out. It may constitute a definite compensation risk.

This phase of the disease was forcefully brought to our attention by a patient who, though first diagnosed thromboangiitis obliterans in 1932, is still receiving partial disability government compensation, because his symptoms supposedly began during his service in the First World War.

When the draft boards refer men for special investigation because of a history of suspicious peripheral vascular symptoms, we now follow a special routine of study for the recognition of early or incipient stages of thromboangiitis obliterans. This means before the usual criteria for diagnosis are present; namely, intermittent claudication, erythromelalgic symptoms, decrease of arterial pulsations, polycythemia, lowered plasma volume and low chloride concentration. Our special routine of study now is the outgrowth of observation and investigation of the peripheral vessels of some 4,000 patients in the past 14 years. These included patients with hypertension, arteriosclerosis, Buerger's disease, multiple sclerosis, retinitis pigmentosa, Raynaud's disease, hypothyroidism, thrombophlebitis and erythromelalgia. The actual number of thromboangiitis obliterans cases in this group is not large, 61, but oddly enough, there have been seven in the past seven months, including four reported later, three draftees referred for study and one boy of 19 in the Michigan National Guard.

Plan of Study

1. Routine Preliminary Examination. To begin with, the usual complete physical examination is carried out. Special attention is given to color changes in the skin of the feet when elevated or dependent, and to arterial pulsations, remembering that in the incipient stage of thromboangiitis obliterans, the pulses may be normal. History, so valuable in the average

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patient coming for medical attention, should not be relied upon too much because of the possibility of willful draft evasion. We also make every effort to exclude arch trouble or foot deformity as the cause for symptoms.

2. Capillaroscopy. Our next step is the examination of the capillaries of the skin at the nail fold. The disease under discussion affects arteries, veins and capillaries, and it is our experience that even the early cases show very characteristic capillary changes. Capillaroscopy is described in the literature early in this century especially in foreign medical publications. For example, in 1922 Mueller [1] compared the capillaries in human skin in days of health and illness. In the same year Hagen [2] described human capillaries under various conditions. In our own country Brown [3] described capillaries in Raynaud's disease as early as 1925. Between these early years and the present time there are several other reports on the appearance of human capillaries. To mention a few, Mueller and Parisius [4] were among the first to call attention to the relation of capillary disorders in neuroses; Griffith [5] tells of their abnormal appearance in neurasthenic states; Leader [6] gives us a picture of capillaries in children; Wright [7] tells of the value of their appearance in various disease conditions; Griffith and Collins [8] mention capillaries in blood pressure studies; Bordley, Grow and Sherman [9] describe capillaries in negroes; Olkon [10] tells of their appearance in schizophrenia; Deutsch [11] again describes in detail capillaries in Raynaud's disease; and Zondek, Michael and Katz [12] tell of capillaries in myxedema.

The method of capillary study used by the various writers is much the same, but we would refer especially to the method of Duryee and Wright.[13] Our apparatus for viewing capillaries is a simplified model of that described and used by these authors. In addition, we have a comfortable adjustable chair in which the patient is seated with the feet on a movable platform just the height of the microscope stage. The platform may also be placed on a table with the microscope if finger capillaries are to be studied. Light to be reflected from the skin area studied is obtained from a small special bulb and a thin blue glass filter so that only white light is obtained. A resistance coil between the wall plug and the bulb makes it possible to use the regular current.

Because of the greater surface available, the great toes are used. The skin proximal to the nail is gently cleansed with green soap and water and then dried. This is important since even slight irritation may change the appearance of the capillary field. Mineral oil is then applied to the area to be examined. This diminishes the refraction due to unevenness of the outer layer of epithelium.

A metal sleeve or trough on the microscope stage helps to steady the toe, so that the capillaries may be easily studied with the lower power of the microscope and 10x eyepiece. The examination is carried out at room temperature with the patient under as nearly normal resting conditions as possible, usually in the morning but not fasting, and before the use of tobacco that day, or any other substances that might abnormally influence the usual capillary flow or shape.

Naturally one must be very cautious in the interpretation of the capillary loops seen because of a rather wide range of so-called normal. We have already referred above to descriptions of several writers. Our observations, however, have been like those of Leader,[6] namely, that in normal young

FIG. 1. Normal capillary picture at nail bed (Mueller).

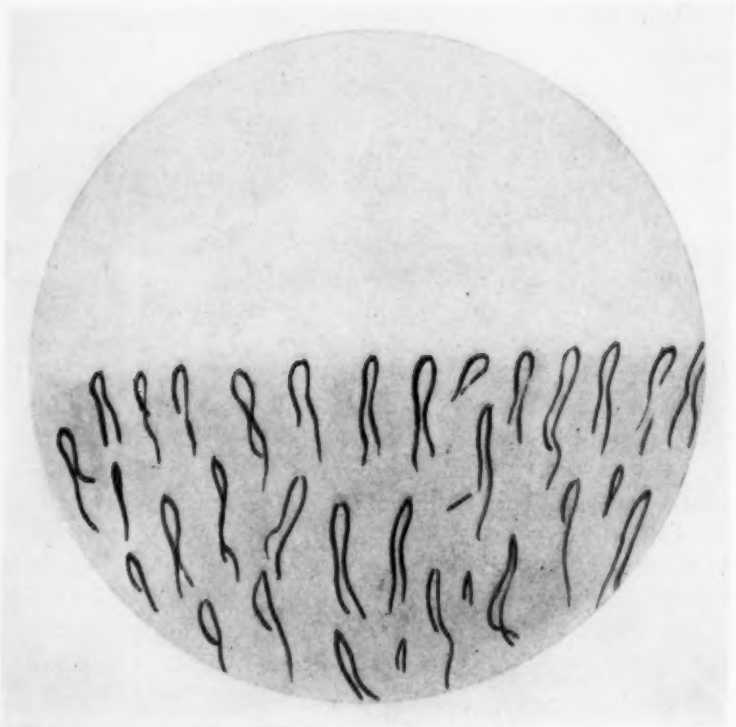

FIG. 2. Drawing of capillaries at nail bed of great toe in normal healthy male of 30 years.

adults, the distal or terminal capillaries show only slight variations from the expected hairpin-shaped loops, with more or less regular or rhythmic blood flow. Longer and shorter loops are both classed as normal. Figure 1 shows a normal capillary picture at the nail bed in children as described by Mueller. Figure 2 is the picture seen in normal young adults, being a drawing by one of us (N. P. D.) of capillaries as actually observed at the nail fold of the great toes.

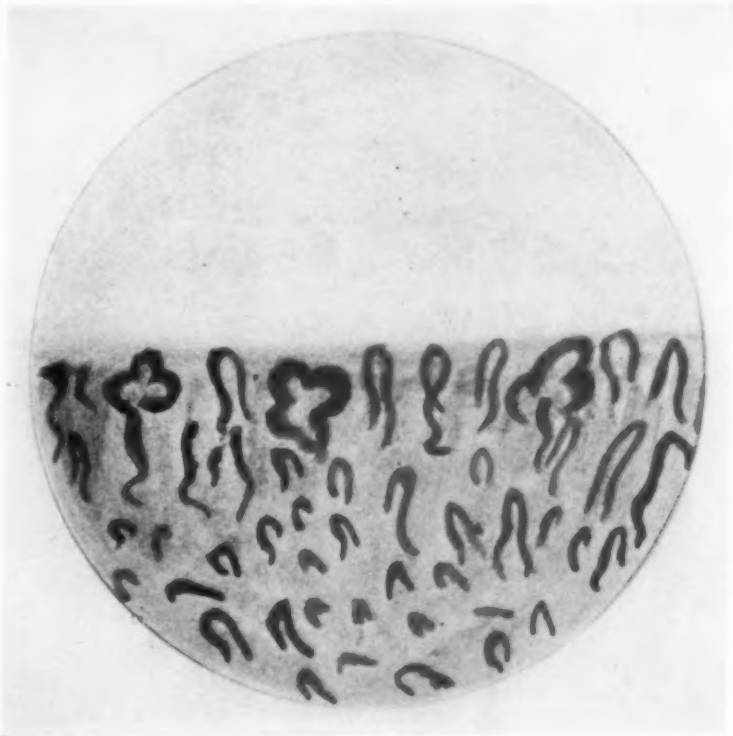

FIG. 3. Drawing of capillaries at nail bed of great toe in young draftee with early thromboangiitis obliterans.

When there is impaired blood flow as, for example, in venous stasis or thyroid gland deficiency, there is some dilatation of the capillary loops, but the general shape still follows the normal pattern. But in young men with even early thromboangiitis obliterans, other disease conditions being excluded, there is a distinctly different and characteristic picture. Many of the loops are distorted, some showing so-called figure-of-eight tortuosity, others being rosette-shaped, somewhat like a coiled hair. These distorted loops invariably show dilatation and in them the blood flow is sluggish or worm-like. Scattered among these abnormally shaped loops may be some quite normal in shape, but with the arterial side narrowed and showing what is interpreted as spasm; namely, blood cells flowing through in spurts or giving

a segmented or beaded appearance. Then, proximal to the area above described the field is dotted with very short partial loops or "nubbins" as we have termed them. This picture is distinctly different from the usual somewhat tortuous but elongated, thinner-appearing capillaries of arteriosclerosis. Figure 3 illustrates our description of capillaries in early thromboangiitis obliterans and figure 4 those in arteriosclerosis. Both are drawings from actual observations, again made by one of us (N. P. D.).

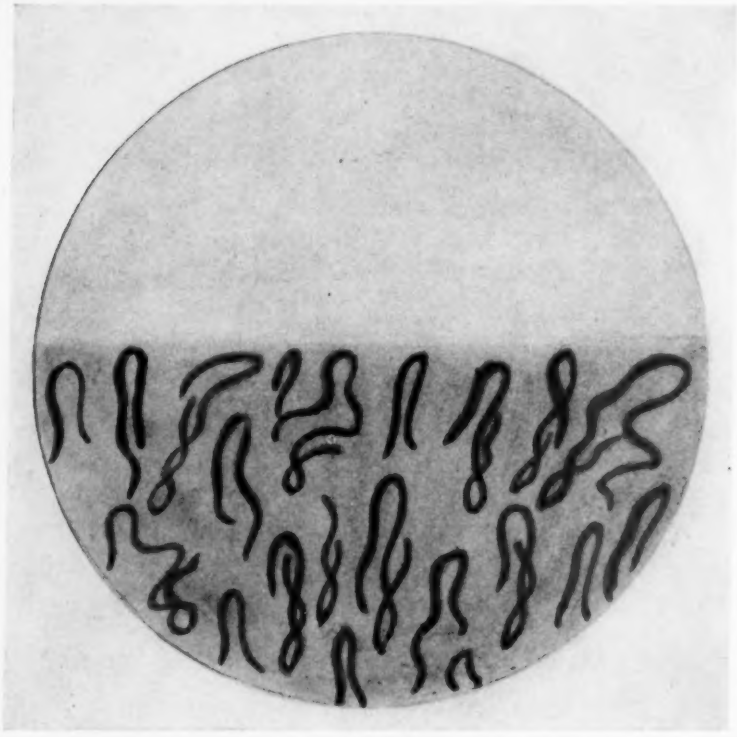

FIG. 4. Drawing of capillaries at nail bed of great toe in male of 62 years with arteriosclerosis.

We have observed somewhat similar tortuosity with rosette shapes and dilatation in several young patients with multiple sclerosis, but these are more often seen in women, there is no vascular occlusion, and other diagnostic data suffice to exclude thromboangiitis obliterans. These were interesting observations, nevertheless, and are to be studied further. We have been able to find only one reference to capillaries in multiple sclerosis.[14]

3. Skin Temperature Response to Cold and Heat. The next step in our plan of study is to determine if there is any vascular occlusion, by taking skin temperature readings by our modification of the method of Gibbon and Landis.[15, 16] The patient is placed in a cool room, temperature between 60° and 65° F., with the feet and legs bare, the remainder of the body being kept

comfortably warm with blankets. The same chair is used as for capillary study. After exposure of the feet and legs for half an hour, the skin temperature of the dorsum and great toes is measured thermoelectrically. Temperature readings are repeated at five minute intervals and when a stable temperature level is obtained, one forearm is immersed in water at from 110° to 114° F., in a thermostatically controlled water bath.* Skin temperature readings are again taken at five minute intervals until a maximum rise is reached, or for at least one hour.

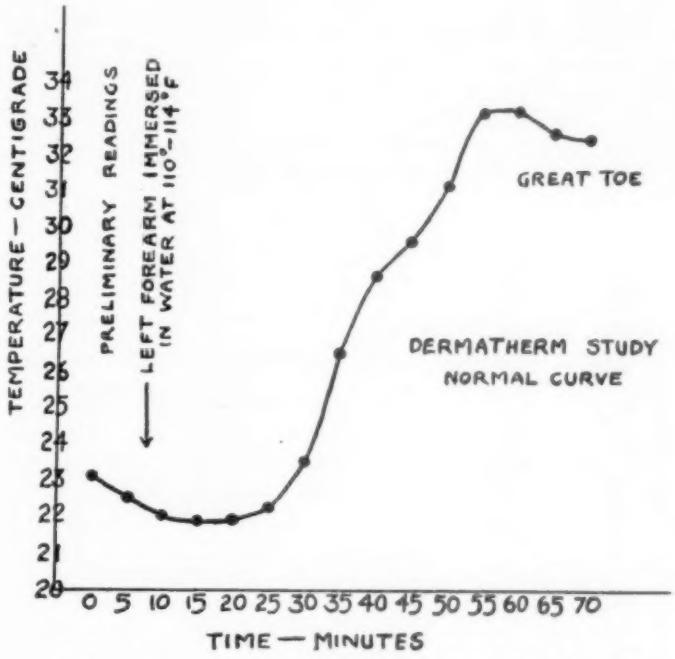

FIG. 5. Normal skin temperature response to cold and heat.

In the earlier years of our skin temperature studies, readings were taken with the dermatherm after cooling the feet and legs as above, and then after spinal anesthesia. We have selected the modified Gibbon and Landis method, however, because it is much simpler and safer so that it can easily be carried out by a junior assistant, is essentially as satisfactory as spinal anesthesia, and more so than oscillometry.

In the normal or purely functional vasospastic individual, vasodilatation begins within 15 minutes and reaches a maximum of above 32° C.—at times 34° C.—within one half hour. Such a response excludes the possibility of obliterating structural disease of the arteries. A normal curve of temperature response is shown in figure 5.

* The self-regulating, thermostatically controlled water bath was designed and constructed at the Henry Ford Hospital with the technical assistance of Mr. A. Krolicki, Chief of the Maintenance Division.

In thromboangiitis obliterans there is invariably evidence of obliteration or occlusion in at least one lower extremity. In early cases such occlusion or diminished ability of the arteries to dilate may be only slight, so that this study is sometimes but not constantly of help in the incipient stage of the disease. This will be shown in the curves of temperature response, or *dermatherm study,* as we call the procedure, in the three draftees and one national guard member mentioned above.

Case Reports

Case 1. F. N., a single Jewish draftee of 26 years, was studied because of the complaint of aching in the feet with some sensitiveness of the skin to touch. At times there was also slight aching in the arms and hands. There was bluish discoloration of the skin of the feet in the dependent position. The toes felt cold to the examining hand. Elevation of the legs produced slight but prompt blanching of the skin of the feet. Pulses could not be definitely felt in either the dorsalis pedis or posterior tibial arteries, whereas radial and ulnar pulses were normal bilaterally.

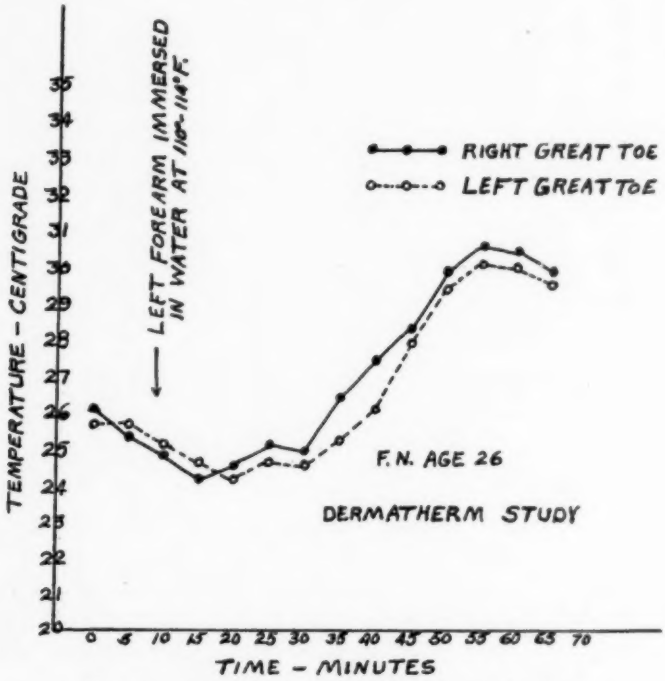

Fig. 6. Early case of thromboangiitis obliterans.

The distal capillaries of the nailfold of the right great toe showed striking tortuosity with some of the loops appearing clumped or in rosette shapes. These were somewhat dilated and blood flow in them was sluggish. Only scattered loops had the normal hairpin shape and in these there was some segmented or beaded flow, evidence of spasm. The left great toe showed a very similar picture except for less dilatation and tortuosity of the terminal capillary loops. On both sides, more proximally there were many of the characteristic short, thickened, partial loops or "nubbins" spoken of above.

Figure 6 shows the result of the dermatherm study in this case. It will be noted that after exposure of the feet and legs in a cool room for 30 minutes the skin temperature level did not drop to as low a level as is often or usually seen. What is more significant, however, is that with heat to one forearm, temperature rise of the skin of the feet was considerably slower than normal or when only vasospasm is present, and also, the total rise was only to a maximum of 30.8° C. on the right and to 30.5° C. on the left as compared with a normal of from 32° to 33° C. In a young man of this age, apparently well in every other respect, such a response makes us feel very definitely that there is already slight arterial occlusion. With the history, physical and capillary findings, the dermatherm study thus helps in establishing the diagnosis.

Case 2. E. R., a single Jewish draftee of 25 years, complained of itching of the skin of the hands and feet with occasional twinges of pain in the feet. There was also some sensitiveness to cold.

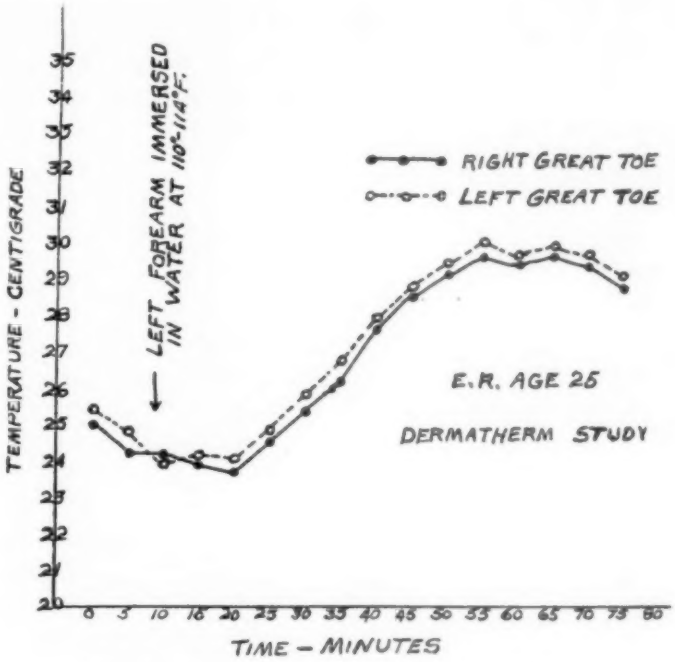

FIG. 7. Early case of thromboangiitis obliterans.

Prompt blanching of the skin of the feet occurred on elevation, but there was no red or blue discoloration when the feet were placed in the dependent position. The pulse was normal in both posterior tibial, but markedly diminished in both dorsalis pedis arteries. Radial pulses were normal.

Capillaries of the right great toe showed moderate tortuosity with occasional rosette shapes and moderate dilatation of the loops with sluggish blood flow. Only slight spasm was noted in the more normally shaped loops occupying about one half of the field. The left great toe showed more tortuosity and clumping of the terminal loops; otherwise it was similar to the right. Again the short "nubbins" were seen in large numbers proximal to the first few distal rows of loops.

The result of the dermatherm study is shown in figure 7. There again is less coldness than is usually seen after exposure in a cool room, the lowest skin temperature reading being 23.6° C. The patient complained of very cold feet at the time and the

skin became very dusky. Following immersion of the forearm in warm water there was quite prompt beginning of temperature rise in the skin of the feet, but again delayed and diminished total rise, almost an hour being required for the maximum temperature rise, and this being again below the normal, namely 29.6° C. on the right and 30° C. on the left.

Case 3. H. H., a 24-year-old draftee of Irish-American descent, was referred because of pain in the arch of the left foot, occurring when standing, or coming on at times after walking a block or two. Shifting his weight to the right foot soon brought relief. Symptoms were no worse in cold weather. There were none in the right foot or leg, nor the upper extremities.

There was quite prompt blanching of the skin on elevating the left leg, less on the right. No definite redness or blueness developed with the foot dependent for a time. Pulsation was normal in both posterior tibial arteries, just palpable in the right dorsalis pedis and absent in the left.

Capillaries of both great toes showed marked tortuosity of the terminal loops for a boy of this age. Most loops also showed dilatation with marked stasis of blood flow. Here and there were narrowed, normally shaped loops with intermittent and segmented flow, interpreted as spasm. Proximal to these loops were numerous incomplete loops or short "nubbins" as in the preceding two cases.

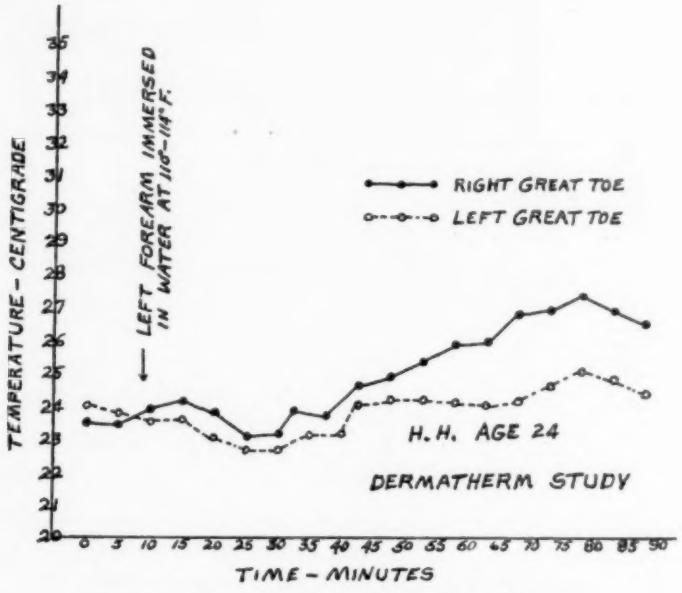

FIG. 8. Early case of thromboangiitis obliterans.

Figure 8 is a graph of the dermatherm study in this case, showing definitely impaired vasodilating ability, more marked in the left, corresponding to the clinical findings. There is confirmation of the spasm noted in the capillaries in that there is considerable delay in response to heat. Organic occlusion is evident from the small total temperature rise of 3° C. on the left and 4.5° C. on the right, and a maximum rise to only 25° C. on the left and 27.3° C. on the right after immersion of one forearm in warm water for more than an hour.

Case 4. R. C., a single boy of 19 years, English descent, one of our former hospital messenger boys, came for advice because of rather severe cramp-like pain in the

right foot and leg and some aching in the left lower extremity while doing guard duty with the Michigan National Guard. More recently, walking only 100 or 200 yards precipitated severe aching in the right calf muscles. Rest relieved this aching quite promptly. There was also some coldness of the feet, not previously noticed. His habits were good except that he was fond of rye bread and smoked a package of cigarettes daily.

The hands and feet were cold to touch. In the dependent position the skin of the right foot was dusky and elevation produced prompt blanching of the skin. Similar less marked changes were present on the left. Pulsations were easily felt in all the peripheral vessels.

Capillary loops appeared the same at the nailfold of both great toes, being normal in number, but showing considerable dilatation of the distal portion and moderate tortuosity. Some segmentation of the flow was noted giving evidence of spasm. Outstanding again were the numerous short "nubbin-like" loops proximally, considered significant in this case especially because of the absence of arterial occlusion by palpation.

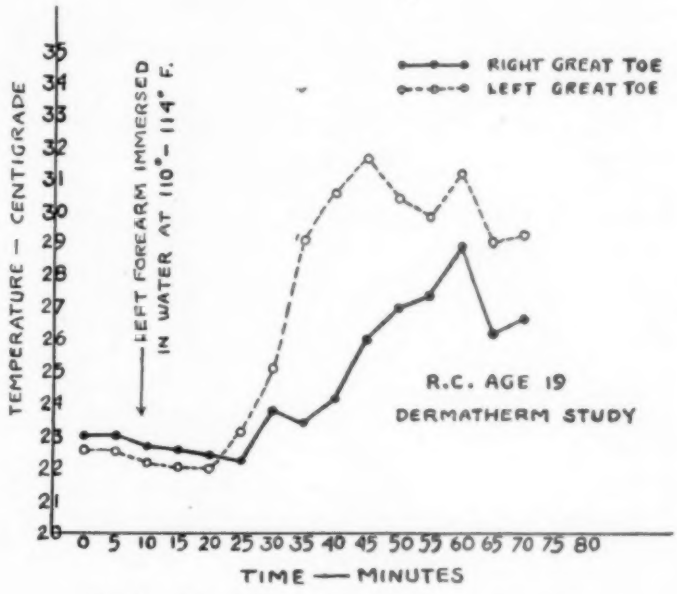

FIG. 9. Early case of thromboangiitis obliterans.

Figure 9 shows rather striking evidence of organic arterial obstruction in the right lower extremity of this patient, even at age 19. It is evidently very early since the maximum temperature rise did reach 29° C. On the left side with only mild symptoms, the rise was still practically normal, 31.5° C. Dermatherm study was felt to be a really important investigation in this case, giving confirmation of our suspicions from the history, the few suggestive physical findings and the capillary findings. It was interesting, too, that abstinence from tobacco made for remarkable improvement in a single week. Despite this response, we always emphasize other significant influencing factors, such as extremes of heat and cold to the feet, ill fitting shoes, careless cutting of callouses or corns, poor habits of eating or resting, and infections of the skin of the feet, particularly trichophytosis.

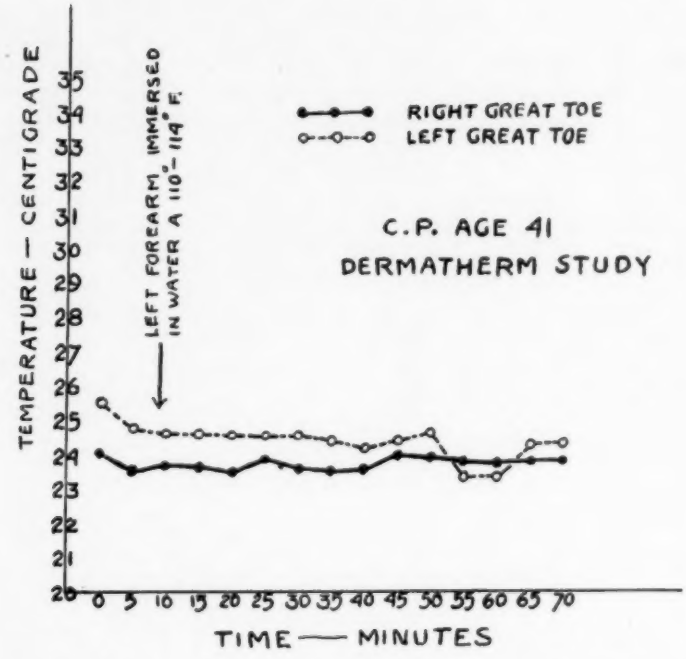

FIG. 10. Moderately advanced case of thromboangiitis obliterans.

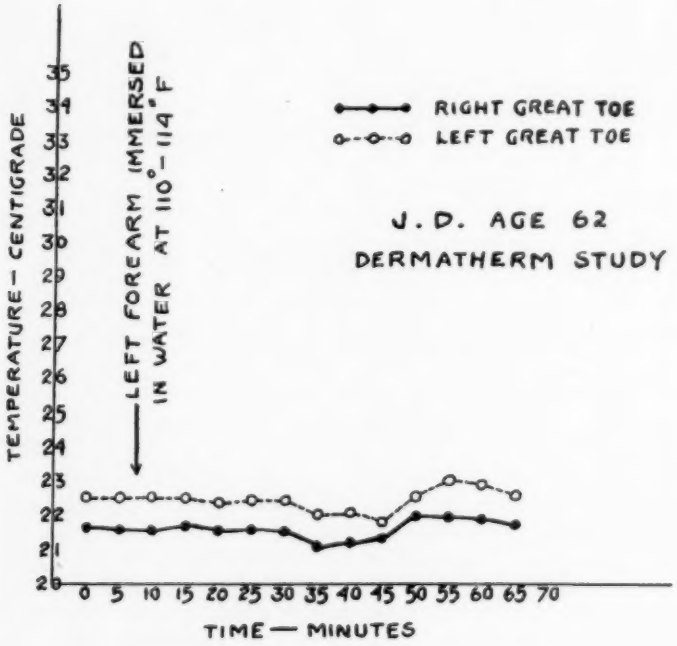

FIG. 11. Case of arteriosclerosis obliterans.

Comment

It will be noted that one foot and leg are invariably more involved than the other, and that a single digit may have symptoms. Yet, at least some involvement of the larger arteries is demonstrated in the slight to moderate organic occlusion revealed by the dermatherm study in each of the four young men reported. None of these cases showed complete occlusion, but such organic obstruction can and does occur in thromboangiitis obliterans even as in the older patient with arteriosclerotic occlusion. Of our 61 cases more than one half gave a dermatherm study response like that shown by the curve in figure 10, one of our recent thromboangiitis cases, aged 41. This is no different from figure 11 which is the curve of a similar study in a man of 62 years with arteriosclerosis obliterans, but naturally these advanced cases of thromboangiitis obliterans require no special study for diagnosis. It is the incipient stage, in a young man between 17 and 21 years of age, in which the diagnosis may be a more difficult problem, and it is in this stage that we have felt the plan outlined to be of definite aid.

Summary and Conclusions

1. Thromboangiitis obliterans occurs in young draftees and should not be overlooked because of possible long continued disability compensation if such draftees are accepted for active service.

2. Incipient stages of the disease may be recognized from the nailfold capillary picture described, together with a modification of the Gibbon and Landis dermatherm study.

3. In these early stages there is diminution in vasodilatation of mild to moderate degree in at least one lower extremity. In the four cases reported the maximum temperature rise in the most involved extremity, after immersion of a forearm in water at 110° to 114° F., was from 2.5° to 4.8° C. below the accepted normal of 32° to 33° C. Later, with more actual occlusion, there is constant coldness of the skin as in arteriosclerosis obliterans and little or no temperature rise on exposure to heat.

4. Two of our patients did not show as low a level of skin temperature as is usually seen after exposure of the feet and legs in a cool room for 30 minutes. We might speculate that with a more active inflammatory process in the vessels in this stage of the disease there might be less vasoconstricting ability. A more likely explanation is the individual differences that are bound to be found in the way of sensitiveness to cold, even with an early disease process present.

5. Having diagnosed the disease early, we should be able to keep these young men reasonably free from symptoms and prevent complications by teaching them more moderate habits of living and meticulous care of the feet.

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APPROXIMATE INSULIN CONTENT OF EXTEMPORANEOUS MIXTURES OF INSULIN AND PROTAMINE ZINC INSULIN *

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The number of possible modifications of insulin is almost unlimited. Within the last few years several new preparations have been described [1, 2, 3] and each has seemed to possess certain more or less specific advantages.[4, 5, 6] Nevertheless, in common with protamine zinc insulin these modifications must of necessity be prepared with definite proportions of ingredients so each has its own individual time-activity, with onset and duration of physiologic action constant for each fixed combination. Each of these modifications provides a curve of time-activity which fits the needs of a limited group of diabetic patients almost perfectly.[6] But judging from the experience when protamine zinc insulin was undergoing its original development in this country and combinations containing various proportions of protamine, of zinc and of calcium were applied clinically, it seems doubtful that any single preparation can be developed within the near future having all desirable attributes and combining rapid and prolonged effects. One alternative would be to devise a series of insulin modifications of varying intensity and duration of action, an event that would doubtless result in untold confusion to patients and physicians alike as well as complicating the marketing of preparations containing insulin.

The majority of diabetic patients can be satisfactorily controlled by soluble insulin if enough doses are given; by single doses of protamine zinc insulin if the total insulin requirement is less than 30 or 40 units per day; or by one injection of protamine zinc insulin and one or more supplementary doses of rapidly-acting insulin in event that the case is exceptionally severe. Various expedients of dietary rearrangement have been advocated in stabilizing patients of the latter group, such as unequal apportionment of meals or variation of the usual intervals between meal times, and the provision of small lunches between meals and at bedtime in order more nearly to adapt the inflow of exogenous carbohydrate to the rate at which active insulin is released from the depot injection of insoluble modified insulin. Recently, evidence [7, 8, 9] is accumulating that injections of extemporaneously prepared mixtures of insulin and protamine zinc insulin permit more highly individualized readjustment of each case since the patient may employ a modification which is "tailor made" to meet varying requirements of onset and duration of insulin effect.

Hagedorn [10] and Krarup [11] first pointed out the possibility of altering the time-activity of protamine-insulin in order to obtain both a quick and a

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long duration of action. Some special modifications of protamine zinc insulin have been under investigation for several years. These contain more or less protamine in relation to insulin content and have different pH values ranging down to the acid side where there is no precipitate but the combination remains in clear solution. Graham [12] and Lawrence [13] used extemporaneous mixtures clinically and reported favorable results, but early experience in this country was not encouraging, probably because the mixtures consisted of too small a proportion of unmodified insulin to protamine zinc insulin. Watson [14] in Canada and Wauchope [15] in England compared the effectiveness of mixtures in patients treated alternately by means of separate injections and then with mixtures. The conclusions were that separate injections of unmodified and protamine zinc insulin led to better control and more economical and accurate balancing. Later Wilder [7] successfully adapted the method, and Ulrich [8] pointed out that by adding sufficiently large amounts of unmodified insulin to protamine zinc insulin, a point is reached beyond which some insulin may be expected to remain. He found by trial that approximately three parts of unmodified insulin to two parts of protamine zinc insulin best served his purpose clinically and that the results were no more unpredictable than those obtained following administration of separate doses of either preparation.

Colwell et al.[9] have developed the method further with more extensive clinical studies and have shown that suitable mixtures of the two standard insulins may be prepared which show any desirable intermediate action, ranging between insulin and protamine zinc insulin in promptness, intensity, and duration of effect. The most generally useful mixture appears to be one made from two parts of insulin to one part of protamine zinc insulin (referred to as a two to one mixture). His series of cases have shown uniform improvement in the number of total injections required, control of glycosuria, avoidance of nocturnal hypoglycemia, and lower average unitage for control.

Because of the wide variability of dietary management in different clinics,

TABLE I

Insulin: Protamine Zinc Insulin Mixtures				Approximate Content of Rapidly-Acting Insulin
Parts				%
Insulin		Protamine Zinc Insulin		
1	:	3	=	10
1	:	2	=	15
1	:	1	=	25
3	:	2	=	40
2	:	1	=	50
3	:	1	=	65
4	:	1	=	70
5	:	1	=	75

as well as variations in individual patients, it is probable that no single fixed proportion will be found suitable for the treatment of all cases. The purpose of this report is to make available some quantitative data that have been accumulated. Peck [16] recently emphasized that the curve of soluble insulin content of such mixtures lies in a zone which may be somewhat variable under the conditions existing when mixtures are prepared extemporaneously. Table 1 gives the approximate zone of insulin content of insulin-protamine zinc insulin mixtures which have been adjusted to the approximate pH of protamine zinc insulin by buffering. Thus far this is the only practical method of assay. In the table the actual figures have been adjusted to the nearest round number. Table 2 is based on these figures and is more useful clinically

TABLE II

APPROXIMATE UNITAGE IN MIXTURES OF INSULIN AND PROTAMINE ZINC INSULIN

	1:①			3:②			2:①			3:①		
UNITS TOTAL	Insulin	(P.Z.I.)	Quick	Insulin	(P.Z.I.)	Quick	Insulin	(P.Z.I.)	Quick	Insulin	(P.Z.I.)	Quick
10	5	**5** = 2.5	**7.5**	6	**4** = 4	**6**	7	**3** = 5	**5**	7.5	**2.5** = 6.5	**3.5**
15	7.5	**7.5** = 4	**11**	9	**6** = 6	**9**	10	**5** = 7.5	**7.5**	11	**4** = 10	**5**
20	10	**10** = 5	**15**	12	**8** = 8	**12**	13	**7** = 10	**10**	15	**5** = 13	**7**
25	12.5	**12.5** = 6	**19**	15	**10** = 10	**15**	17	**8** = 12.5	**12.5**	19	**6** = 16	**9**
30	15	**15** = 7.5	**22.5**	18	**12** = 12	**18**	20	**10** = 15	**15**	22.5	**7.5** = 19.5	**10.5**
35	17.5	**17.5** = 9	**26**	21	**14** = 14	**21**	23	**12** = 17.5	**17.5**	26	**9** = 23	**12**
40	20	**20** = 10	**30**	24	**16** = 16	**24**	27	**13** = 20	**20**	30	**10** = 26	**14**
45	22.5	**22.5** = 11	**34**	27	**18** = 18	**27**	30	**15** = 22.5	**22.5**	34	**11** = 29	**16**
50	25	**25** = 12.5	**37.5**	30	**20** = 20	**30**	33	**17** = 25	**25**	37.5	**12.5** = 32.5	**17.5**
60	30	**30** = 15	**45**	36	**24** = 24	**36**	40	**20** = 30	**30**	45	**15** = 39	**21**
70	35	**35** = 17.5	**52.5**	42	**28** = 28	**42**	47	**23** = 35	**35**	52.5	**17.5** = 45.5	**24.5**
80	40	**40** = 20	**60**	48	**32** = 32	**48**	53	**27** = 40	**40**	60	**20** = 52	**28**
90	45	**45** = 22.5	**67.5**	54	**36** = 36	**54**	60	**30** = 45	**45**	67.5	**22.5** = 58.5	**31.5**
100	50	**50** = 25	**75**	60	**40** = 40	**60**	67	**33** = 50	**50**	75	**25** = 65	**35**
110	55	**55** = 27.5	**82.5**	66	**44** = 44	**66**	73	**37** = 55	**55**	82.5	**27.5** = 71.5	**38.5**
120	60	**60** = 30	**90**	72	**48** = 48	**72**	80	**40** = 60	**60**	90	**30** = 78	**42**
130	65	**65** = 32.5	**97.5**	78	**52** = 52	**78**	87	**43** = 65	**65**	87.5	**32.5** = 84.5	**45.5**
140	70	**70** = 35	**105**	84	**56** = 56	**84**	93	**47** = 70	**70**	105	**35** = 91	**49**
150	75	**75** = 38	**112**	90	**60** = 60	**90**	100	**50** = 75	**75**	112.5	**37.5** = 97.5	**52.5**

as one can determine from it at a glance the approximate relative proportion of rapidly-acting and slowly-acting insulin that will be present in a given mixture.*

*This does not necessarily infer that the time-activity of the quick-acting component is identical with that of standard preparations of unmodified insulin as marketed; likewise, the time-activity of the precipitated component may not be identical with that of standard preparations of protamine zinc insulin.

Clinical experience thus far indicates that the most generally useful extemporaneous mixtures are in the ratio of three to two or two to one parts of insulin to protamine zinc insulin. For practical purposes, mixtures made of equal parts do not show effects significantly different in action from those obtained when using protamine zinc insulin whereas the combinations containing three parts of insulin to one part of protamine zinc insulin result in too short a time-activity and too great an intensity of effect during the daytime. The table of approximate unitage provides a quantitative starting point which we have found useful in making individual readjustments in the direction of greater or lesser insulin activity and duration of effect. These figures are to be regarded as only approximate; several factors may be responsible for variation in either direction. For example, the pH may vary somewhat in different mixtures depending upon the relative amounts of the different preparations used and this may affect the total solubility of the mixture in the tissues. Furthermore, not all patients may be anticipated to respond in an identical manner. There may also be differences in the results obtained when shifting from one manufacturer's lot to another or, more particularly, when using preparations of different manufacturers since these may not always be chemically and physically identical. For these reasons, the greatest consistency of results should be gained by using the same product in the same proportions, and to simplify matters still further, in the same concentrations.

Summary

Two tables are presented to show the approximate range of insulin content in mixtures of insulin and protamine zinc insulin which have been extemporaneously prepared.

It is emphasized that these figures are approximations only and that variations may occur depending upon individual circumstances. These data should be regarded as only a starting point in making individual readjustments of patients.

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THE EFFECTIVENESS OF REPLACEMENT THERAPY IN ACHLORHYDRIA *

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THE diminution or absence of hydrochloric acid in the stomach is not an infrequent occurrence. Among representative studies are those of Bennett and Ryle,[1] who in 1921 observed that 4 per cent of 100 normal, healthy male medical students had achlorhydria, and those made by Vanzant, Alvarez and associates [2] who in 1932 found achlorhydria in patients without gastric disease in from 25 to 35 per cent between the ages of 60 to 70 years. More recently Ruffin and Dick [3] studied the gastric acidity of 2877 patients and found lack of acid in 10 per cent of the total and in 25 to 30 per cent of patients over 45.

Although anacidity may occur in persons with no demonstrable gross disturbances in health at the time, it is a matter of observation that it frequently is associated with varied types of functional or organic abnormalities, particularly digestive disturbances and defective alimentation. The rôle that stomach acid plays in normal physiology has frequently been reviewed and the more outstanding functions may briefly be mentioned as pepsin activation, protein swelling, bactericidal effect, motor and secretory activation, and solution of iron. Recently Ivy and associates [4] have shown the important effect of lack of acid on calcium absorption and bone growth after gastrectomy in young dogs. The question of degradation of thiamine in the anacid stomach has also been recently raised.

It was, of course, natural that replacement therapy with hydrochloric acid should be considered as an ideal solution of this deficiency problem and dilute hydrochloric acid has been widely used in the attempt to correct anacidity. That little was accomplished by the official pharmacopeial dosage of 10 to 15 minims or 1 c.c. with meals was, however, becoming rapidly apparent to various observers. Hurst was one of the first to recognize the inadequacy of the usual dosage and recommended 4 to 6 c.c. This amount, however, is generally considered impractical and it is the common experience that patients will refuse to take it for any length of time. Crohn [5] and Kern, Rose and Austin [6] have shown that the usual doses of dilute hydrochloric acid are ineffective in appreciably modifying the gastric acidity in achlorhydria. The detrimental effects of large doses of hydrochloric acid on the system in general, on the kidneys, and particularly on the teeth, as recently discussed by Staphne,[7] have been duly considered. In regard to renal irritation and systemic effects it must be recalled that the normal

* Read at the St. Paul meeting of the American College of Physicians April 24, 1942.
From the Santa Barbara Cottage Hospital and The Sansum Clinic, Santa Barbara, California.

stomach acid, although secreted in far greater amounts than any therapeutic dose ever suggested, is neutralized, resynthesized and resecreted in a cycle whereas orally administered hydrochloric acid is wholly excreted and in absence of good excretion may be accumulated.

Various suggestions have been made to overcome the disagreeable and detrimental effects of oral hydrochloric acid administration, and to this end glutamic acid hydrochloride which can be taken in capsules has been used. Shay and Gershon-Cohen [8] reaffirmed the ineffectiveness of as much as 80 drops (about 5 c.c.) of dilute hydrochloric acid when added to the usual Ewald meal (20 gm. Zweiback in 300 c.c. water) on the titratable acidity and pH of the stomach contents in patients with anacidity. These authors, however, found that four 310 mg. capsules of glutamic acid hydrochloride lowered the gastric pH to about 2.5 in two cases. It must be borne in mind, however, that such a "meal" of 20 gm. Zweiback contains only 3 gm. protein and in no way compares with the average largest meal of a day of about 40 gm. or even as much as 60 gm. protein.

The use of citric acid (1 dram powder dissolved in 60–100 c.c. water, or 60 c.c. of lemon juice has been advocated by Sansum and Gray [9] instead of hydrochloric acid. This organic acid has the advantage, particularly in the form of lemon juice, of being more palatable and of being subsequently destroyed in the body, thus avoiding renal irritation and the possibility of systemic acidosis. No data are available, however, on the effectiveness of this form of replacement as far as the specific physiological functions of normal acidity are concerned.

Purpose of Study

Our approach to this problem has been to evaluate acid replacement therapy from the standpoint of the actual lowering of the pH in the presence of a *normal meal* and the effectiveness of such lowering as related to several of the known physiological functions of normal gastric acidity. In this respect we have studied the effect of replacement therapy on pepsin activation, protein swelling, bactericidal action, calcium solubility and restoration of normal gastric pH.

Methods

The test meal was selected from the standpoint of duplication of a normal meal and of precise reproducibility. Table 1 gives the composition of the meal used. The ingredients were ground twice in a fine food chopper to a semifluid state. The mixture in a vessel was placed in a constant temperature water bath at 37.5° C. and agitated by an electric stirrer. The calomel and glass electrodes for pH determinations were submerged in the mixture and connected with extended shielded cables to a Beckman pH meter corrected to read at 37.5° C. The various acids were then added gradually in small amounts from a burette and repeated pH readings made until constant values were obtained before more was added.

TABLE I

Special Test Meal, 558 Calories

Food	Gm.	Carbohydrate	Protein	Fat
		gm.	gm.	gm.
Milk	240	12.0	7.2	9.6
Bread	32	16.0	3.2	
Meat (lean ground steak)	100		20.0	9.2
Beans (canned green string)	100	6.0	2.5	
Peaches (juice packed)	100	9.2		
Potato (baked)	100	18.0	3.2	
Water	100			
Total	772	61.2	36.1 *	18.8

* Actual protein found 40.8 gm.

Such experiments in vitro have certain advantages over ingestion and aspiration tests, for reproducible curves with large numbers of readings can be obtained and the complicating factor of loss of unknown amounts through the pylorus is avoided. Two factors, however, are not taken into account, the effect of mucin secretion by the stomach mucosa, and the possible regurgitation of alkaline duodenal contents. Both of these factors, however, one by buffer effect and the other by neutralization would tend to require increased amounts of acid in vivo and consequently the amount of added acid to bring about a certain lowering of pH may even be greater than in vitro experiments indicate.

RESULTS

The Effect of Acid Addition to a Normal Meal and Its Relation to Normal Gastric pH and Pepsin Activity. The effect of added acid on the pH of a normal meal is shown in figure 1, on which is also shown the normal gastric post-meal pH range of 1.6 to 1.8 (Shohl and King,[10] Haggard and Greenberg [11]). Our findings showed that with the normal test meal one half to one and a half hours after its ingestion the pH of aspirated gastric contents in eight normal cases ranged from pH 1.4 to 1.8. It is readily seen from our titration curves that no amount of acid that can practicably be taken will lower the pH of a meal to normal levels. No amounts of glutamic acid hydrochloride, citrus acid or lemon juice used reached this range. It took 104 c.c. normal hydrochloric acid which are approximately equivalent to 34 c.c. or 510 drops of dilute hydrochloric acid U.S.P. to bring the meal pH to the normal physiological level. Even the large doses of 5 c.c. of Hurst and Shay and Gershon-Cohen brought the pH of the meal down to only 4.3.

PEPTIC ACTIVATION

That pepsin is only active at low pH values has long been known. On figure 1 is indicated the relation of pH to peptic activity at 37.5° C. on egg albumin as obtained by the Mett tube method. These values are very simi-

lar to those obtained by Northrop [12] measuring amino nitrogen liberation. The optimum peptic activity varies somewhat with various proteins, depending upon their isoelectric points, but the effect of different acids is nearly altogether dependent upon their hydrogen ion dissociation. It is readily seen from the chart that acid substitution therapy in practical amounts can in no way bring about the activation of pepsin.

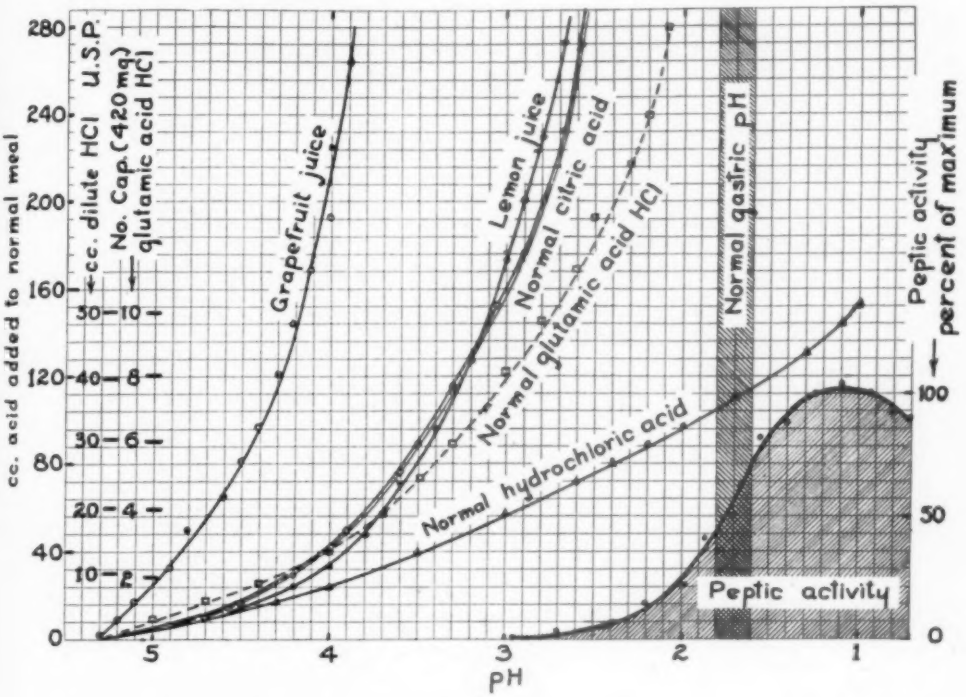

FIG. 1. The relationship of the addition of acid to a representative meal and the resultant pH. The relationship of peptic activity to pH and the normal post-meal gastric pH range are also superimposed on this figure.

Relation of Amount of Acid Required to Protein Concentration of Meal. The reason for the large amount of acid necessary to bring the pH of a meal to the normal gastric post-feeding pH is, of course, the buffer capacity of the meal. Carbohydrate and fat have relatively little buffer value and consequently this effect is due largely to the protein content. Figure 2 shows the amount of hydrochloric acid required to bring 100 gm. of different ground foods in 100 c.c. water to various pH values. It will be noticed that, as would be expected, the amount of acid necessary to bring about a certain change for different foods varies greatly, from 2.5 to 34 c.c. 1.0 normal acid or approximately 0.8 to 11 c.c. U.S.P. acid. Figure 3 illustrates the relationship of acid to protein by showing the amount of acid required to bring 100 gm. of various foods to pH 2.0 as obtained from the data of figure 2. The

amount of acid required is practically a linear function of the protein concentration regardless of the nature of the foodstuff. This relationship emphasized the necessity of the use of a normal meal or at least the protein equivalent of a normal meal to study acid replacement effectiveness. The Ewald test meal of 20 gm. Zweiback with a protein content of 3 gm. as used by Shay and Gershon-Cohen in their replacement studies gives a highly erroneous impression inasmuch as the average large meal of the day contains from 40 to 60 gm. protein. Consequently it would take from 13 to 20 times greater an amount of hydrochloric acid or glutamic acid hydrochloride than these authors found for effective therapy.

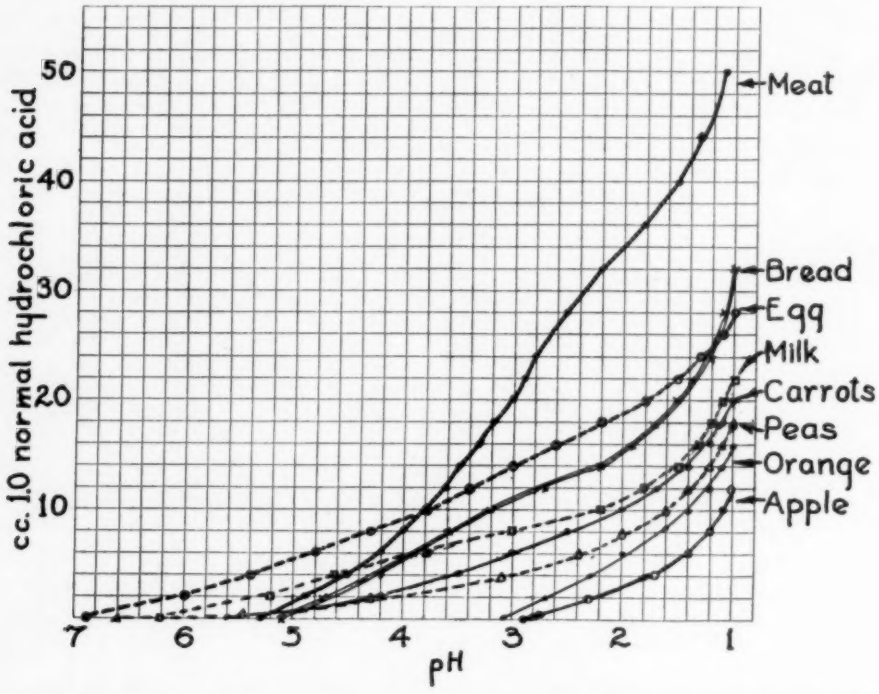

FIG. 2. The pH values of 100 gm. of various foods brought about by the addition of various amounts of hydrochloric acid.

The Effect of pH on Protein Swelling. That acids cause hydration and swelling of protein colloids has long been known. It is believed that such hydration and swelling facilitate solution and the penetration of the digestive enzymes. Loeb [13] has shown that the degree and maximum swelling of a protein in acid solution is proportional to the hydrogen ion concentration. Pure gelatine, for example, was found to have a maximum swelling at pH 3.2 and a minimum at its isoelectric point of 4.7. In figure 4 is presented the relative swelling of commercial gelatine and casein, of unpurified coagulated egg albumin, and the test meal used in our studies. The meal, egg albumin

and casein had a maximum swelling that coincided approximately with the pH of the contents of the normal post-meal stomach. Commercial gelatin had a maximum swelling at pH 3.0 which is a little lower than that found by Loeb (3.2) for pure gelatin. It is to be noted that the proteins had a minimal swelling (least desirable for digestion) at approximately their isoelectric points, pH 4.0 to 5.0, and the minimal volume for the meal solids also fell within this range. This pH range is about that obtained by the usual acid doses in replacement therapy in achlorhydria with a normal meal and, consequently, as far as swelling is concerned, the usual acid therapy may actually retard digestion. The normal post-meal stomach contents have a pH that gives optimal protein swelling, and replacement therapy to have a maximal effect would have to lower the pH below 2.0.

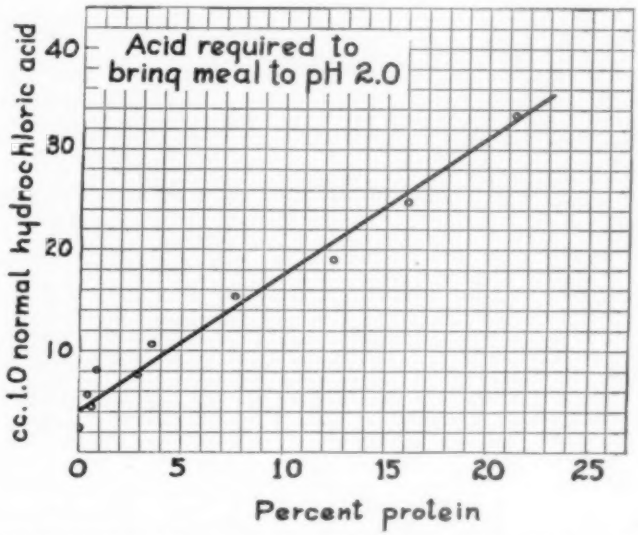

FIG. 3. The acid required to bring the pH of 100 gm. of various foods of different protein content to pH 2.0.

*Bactericidal Effect.** An extensive study of the bactericidal effect of the gastric acidity has not been undertaken. No attempt was made to study the resistance of especially acid resistant strains of organisms, spores, or lipid encapsulated bacteria, as for example, the tubercle bacillus type. A few of the common organisms were, however, tested to show the acid effect. The standard meal was brought to various pH values with 0.1 N hydrochloric acid as described above. Small aliquots were taken at the different pH values, and to these 0.5 to 1.0 c.c. of 24 hour broth cultures of the various organisms were added. After mixing the specimens were incubated at 37° C. for three hours. Loopfuls of material were then streaked on sterile one sixth blood agar plates. No growth is indicated as 0 and heavy growth as ++++ in table 2.

* The bacteriological work was done by Mrs. Elsie Ferrell.

It will be noted that for certain organisms as *E. coli*, only pH values materially below 2.0 on 3 hour incubation had any marked destructive effect. Since three hours or less is about the average length of time that food remains in the stomach, it seems that a complete lowering of the pH of the stomach contents to normal levels may be necessary for complete or nearly complete

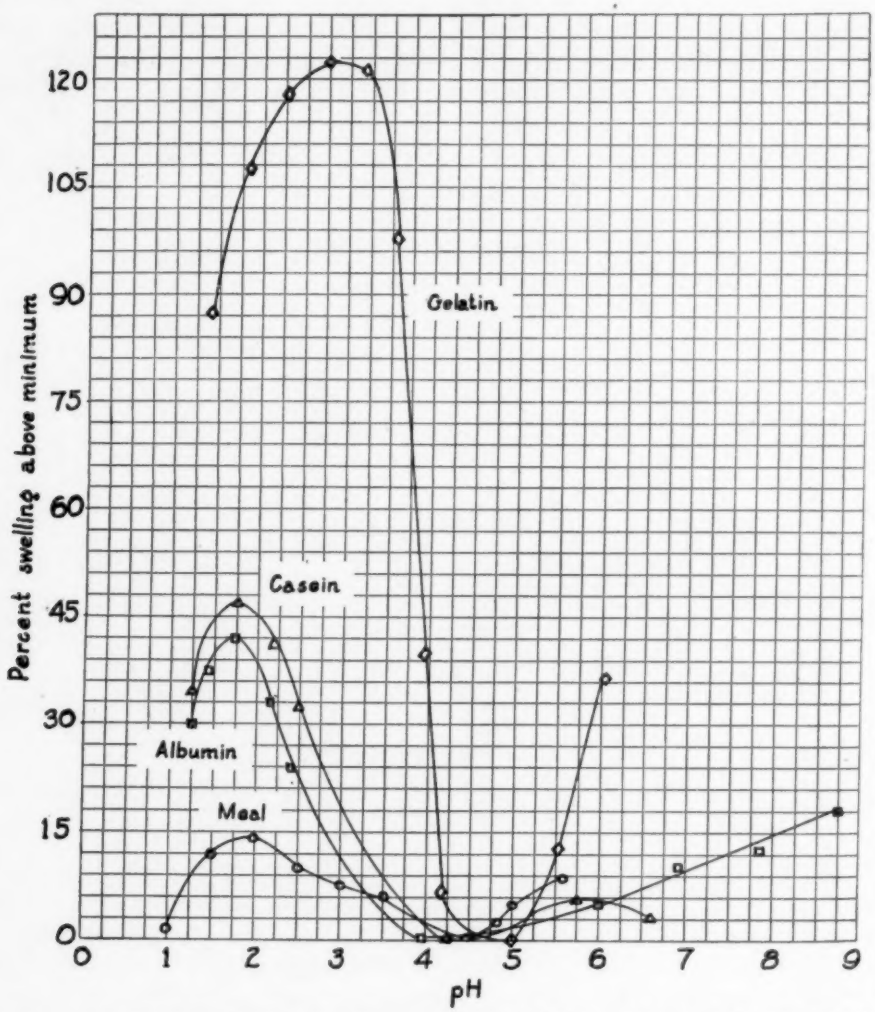

FIG. 4. The per cent swelling above minimum volume of different foods at different pH values brought about by addition of acid or alkali.

bactericidal effect. Somewhat similar findings were obtained with a strain of *Staphylococcus aureus* and also with a non-pigmented staphylococcus, although these organisms were apparently a little more sensitive to acid. Certainly any acid replacement therapy in achlorhydria would not lower the pH of a meal sufficiently to have effective bactericidal action as far as these

TABLE II

The Effect of pH of Meal on Destruction of Bacteria

Non-pigmented Ahemolytic Staph.		*Staph. aureus*		*E. coli*		Beta streptococcus	
pH	Growth	pH	Growth	pH	Growth	pH	Growth
5.6	++++	5.7	++++	5.5	++++	5.8	++++
5.0	++++	5.3	++++	4.9	++++	5.0	++++
4.0	++++	4.6	++++	4.5	++++	4.5	+++
3.4	++++	3.9	+++	4.0	+++	4.0	±
3.0	++++	3.5	+++	3.6	+++	3.5	0
2.5	++++	2.9	+++	3.0	+++	3.0	0
2.0	+	2.6	+	2.4	+++	2.5	0
1.5	+	1.9	0	2.0	+++	1.9	0
1.1	±	1.5	+	1.4	0	1.4	0

organisms are concerned. On the other hand, certain organisms, and probably these include some of the more pathogenic bacteria such as the strain of beta streptococcus shown in table 2, are definitely destroyed under these conditions at pH values below 4.5. Such effective values could be reached with four to six 420 mg. capsules of glutamic acid hydrochloride or about 60 c.c. of normal citric acid or lemon juice. In all probability certain pathogenic spores or encapsulated organisms could tolerate extremely low pH values.

The Effect of pH on Calcium Solution. On an adequate dietary calcium intake (0.7 gm.) the greater part of the calcium is furnished by milk and is consequently bound to protein. Van Slyke and Baker [14] showed that the calcium was liberated from casein by acid addition and that this solution increased up to the isoelectric point of casein (pH 4.7) when all calcium was freed. Holt, La Mer and Chown [15] have shown that as the various calcium phosphates are acidified, complete solution takes place below pH 5.0. Ivy and associates [4] have shown that stomach acid is essential for normal bone structure, at least in the growing animal.

That in the solution of calcium salts a time factor exists has frequently been appreciated and was again emphasized by Holt and coworkers for the calcium phosphate systems. We have checked the splitting of calcium from casein at different pH levels under conditions as found in the stomach. Ten c.c. milk were curdled with renin at 37.5° C. for 30 minutes. Acid was then added to obtain the desired pH values, the volume was diluted to 15 c.c., and incubation continued with gentle shaking for another three hours. The mixtures were filtered to obtain the soluble calcium, the filtrates were all brought to pH 7.0, and the phosphates were removed with ferric chloride and calcium determined according to the method of Hoffman.[16]

Figure 5 shows the soluble calcium split from milk curd at various pH values obtained by hydrochloric and citric acid additions at the end of a three hour agitation at 37.5° C. The importance of adequate lowering of the pH of the gastric contents for calcium liberation can readily be seen. Under

these conditions there was little if any difference between the effect of hydrochloric or citric acid at any given pH. It will be noted, however, that under conditions of complete equilibrium (Loeb, Van Slyke et al.), all calcium should be liberated at pH 4.7, the isoelectric point of casein. This was not the case, however, for a three hour period of incubation (the average emptying time of the stomach), for calcium liberation was found to be moderately slow but was increased by lowering the pH. In conditions of rapid emptying time of the stomach the amount of calcium liberated is proportionately decreased.

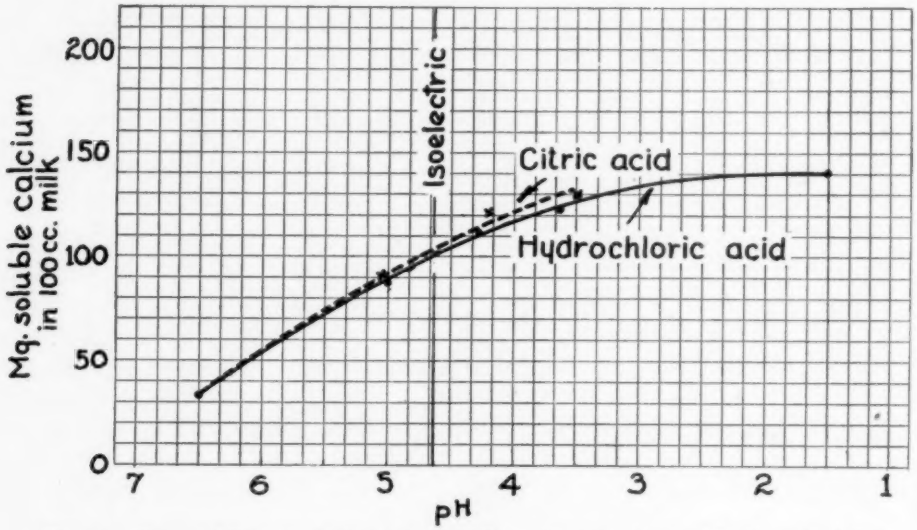

FIG. 5. The solubility of calcium from curdled milk at various pH values in three hours at 37.5° C.

The Effect of Anacidity on Thiamine Stability. Since thiamine is destroyed in alkaline solution exposed to oxygen and stability is promoted on the acid side, the question of destruction of thiamine in anacidity has been raised. The work of Melnick, Robinson and Field,[17] however, has shown that thiamine is stable in normal gastric juice from pH 1.5 to 8.0 during a 16 hour incubation at 37.5° C.

The Probable Amount of Acid Secretion in the Stomach. Since the amount of hydrochloric acid secreted by the stomach for a meal must be enough to bring the pH value to about 1.8 or lower, this amount should be approximately comparable to the 104 c.c. normal hydrochloric acid that was required to bring the pH of an average meal to this pH in our experiments. The average meal would accordingly require about 3.8 gm. hydrochloric acid. The actual amount, however, must be considerably more, for digested protein has an increased buffer capacity, gastric mucin has an additional buffer value, and alkaline regurgitation from the intestines (said to be a normal process [18]) would result in partial neutralization. The lower values

usually considered normal for acid secretion are based on inadequate test meals (toast and tea) and consequently on only partial stimulation of acid secretion. From a practical standpoint, the effect of food on gastric acidity is a summation effect of the acid stimulating and acid neutralizing abilities of the various dietary constituents as well as the emptying rate of the stomach.

Conclusions and Summary

1. The addition of acid to a representative ground meal at body temperature in vitro shows that the usual amount of acid used in replacement therapy has but little relative effect on the pH of the meal, because of the buffer value of the food. The amount of any acid necessary to bring the pH of a meal to the normal physiological post-meal range (pH 1.6 to 1.8) or for peptic activation (below pH 2.0) is of such magnitude that practical aspects preclude its administration. For U.S.P. hydrochloric acid this amount would be 35 c.c. Even twenty 420 mg. capsules of glutamic acid hydrochloride with a meal would fail to produce normal acidity or activate pepsin.

2. Upon acid addition, different foods have a buffer or neutralizing effect approximately proportional to their protein content. For this reason an average large meal may have from 15 to 20 times the neutralizing ability of the usual Ewald test meal of 3 gm. protein. Consequently the evaluation of acid replacement therapy with an Ewald meal may give altogether erroneous results.

3. Except for gelatin, the swelling of proteins as a step in solution and digestion is not appreciably influenced by even the largest doses of acid advocated in replacement therapy. In fact, the usual doses of acid advocated bring the pH of a meal to the range of minimum swelling of the proteins.

4. Usual acid replacement therapy does not bring the pH sufficiently low to have any appreciable bactericidal effect. Certain strains of staphylococci and coli are uninfluenced by exposure in a meal to the maximum amount of acid therapy practical. In fact, only complete attainment of the normal post-meal gastric pH gives anywhere nearly complete bactericidal action, and even this pH may not be effective within the normal emptying time of the stomach for certain acid-resistant, encapsulated or sporulated organisms. On the other hand, certain types of pathogenic organisms are very sensitive to even slight lowering of the pH below neutrality and acid therapy might well be a factor in their destruction.

5. Decreasing pH values from 6.5 to 1.5 are instrumental in proportionally increased liberation of calcium from milk over a three hour period. On the basis of complete equilibrium, maximum calcium liberation should occur at the isoelectric point of casein, pH 4.7, but during a three hour period of incubation complete equilibrium has not been obtained and further lowering of the pH results in more rapid liberation of calcium.

6. Anacidity or hyperacidity has no effect on thiamine destruction.

7. The amount of hydrochloric acid secreted by the stomach for an average meal must be in excess of 104 c.c. normal, 35 c.c. U.S.P., or 3.8 gm. as calculated from our data.

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A METHOD FOR THE CONTINUOUS RECORDING OF GASTRIC pH IN SITU. IV. FURTHER EVALUATION OF THE EFFICACY OF ANTACIDS IN VITRO AND IN THE HUMAN BEING*

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A method for the continuous recording of gastric pH in situ was recently described [1, 2] and utilized in providing continuous pH recordings in vivo (dogs) and in vitro. Sodium bicarbonate, Sippy A powders, magnesium trisilicate, magnesium superoxol, and aluminum hydroxide were tested.[3] The present communication deals with titrations in vitro and in the human stomach of these and other antacids commonly used in ulcer therapy.

Materials and Methods

In Vitro. Thirty c.c. of 0.1 normal hydrochloric acid and 70 c.c. of distilled water were placed in a beaker to represent the fasting contents (pH 1.4) of a hyperchlorhydric human stomach. This solution was led by rubber tubing to a glass electrode connected to a continuous pH recorder. A pumping system previously described [2] was used to maintain circulation of the mixture around the glass electrode. After a 10 minute control period the antacid, made up to 100 c.c. with distilled water, was permitted to flow over the glass electrode which was then washed by 50 c.c. of distilled water. One tenth normal hydrochloric acid was added to the beaker at the rate of 120 c.c. per hour which simulates the secretory rate of the hyperchlorhydric stomach.

In Vivo. Patients on the Second (Cornell) Medical Division, Bellevue Hospital, were chosen as subjects. The fasting subject was seated in a wheel chair with the back sloping 60 degrees. The purpose and safety of the procedure were explained, after which the soft palate and pharynx were anesthetized by the application of a 2.0 per cent pontocaine solution containing one part in 20,000 adrenalin hydrochloride. Five minutes after the application of pontocaine the stomach tube was passed to a distance of 18.5 inches from the incisor teeth, at which level it was kept throughout the experiment. The stomach tube used is illustrated in figure 1. Its lumen contains a small glass electrode with its shielded lead, a potassium chloride reference electrode tube, and reserve space to permit the passage of fluids. The location of the tube tip on the greater curvature just above the antrum was verified fluoroscopically. The subject's stomach was emptied. After determining

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the amount and pH of the fasting contents, a measured quantity was returned to the stomach and the recorder started. When the same subject was used to evaluate several antacids the same quantity was used in each experiment. After a short control period the antacid was added in the manner described for the beaker experiments. On several occasions, because of rapid emptying, additional distilled water had to be added before completion of an experiment in order to keep the glass electrode in a fluid medium. At the end of an experiment the stomach was emptied,

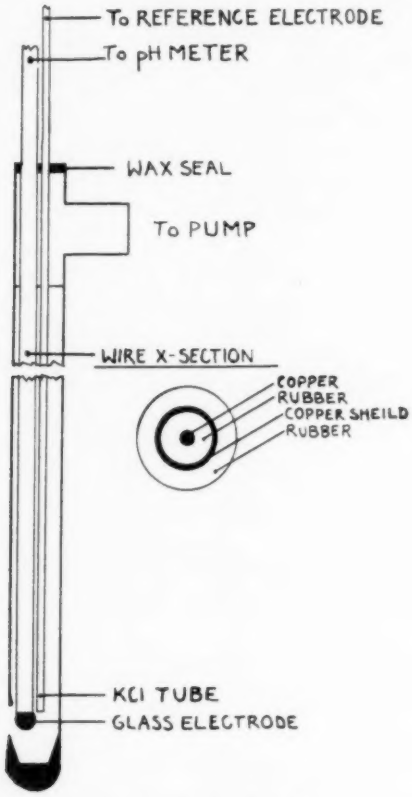

FIG. 1. Stomach tube.

contents mixed, and pH determined with the standard glass electrode. Several recordings also were made using a continuous flow glass electrode to which gastric contents were led by nasal tube.

RESULTS

Figure 2 was made by superimposing the titration curves of the indicated antacids. One gram quantities were used so that the tracings would be comparable. Inspection reveals that calcium carbonate causes the most marked and prolonged rise in pH. In order of decreasing effect the re-

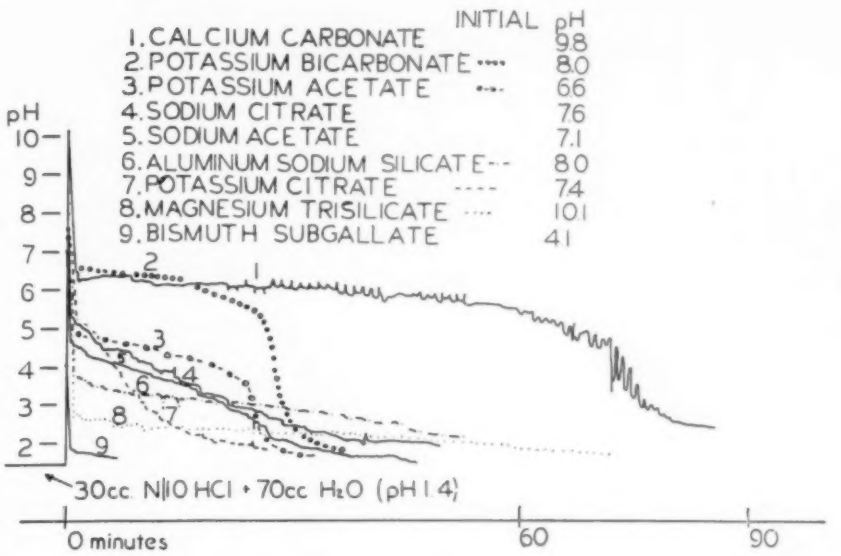

FIG. 2. In vitro.

maining antacids are: potassium bicarbonate, potassium acetate, sodium citrate, sodium acetate, aluminum sodium silicate, potassium citrate, magnesium trisilicate, and bismuth subgallate. Tracings for bismuth subnitrate and bismuth subcarbonate (initial pH 3.9 and 7.0 respectively) were omitted because they were almost identical with the tracing for bismuth subgallate.

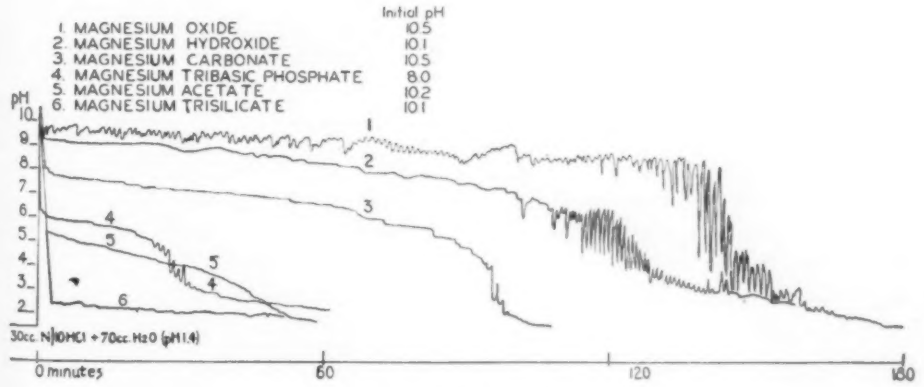

FIG. 3. In vitro.

In figure 3 the titration curves show the pH changes after the addition of 1.0 gram quantities of magnesium compounds. The marked rise in pH caused by magnesium oxide is readily demonstrated. A tracing for magnesium peroxide (initial pH 10.7) was omitted because this followed closely the curve for magnesium hydroxide. In figure 4 curves secured with mix-

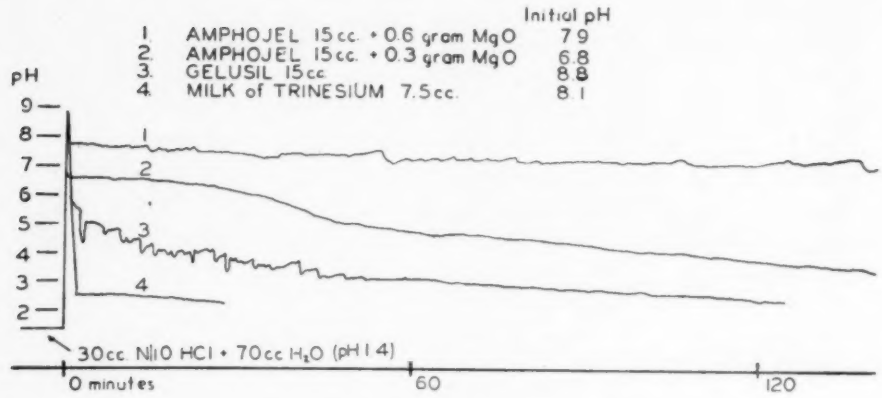

FIG. 4. In vitro.

tures of aluminum hydroxide and magnesium trisilicate (Gelusil and Milk of Trinesium) are shown together with that obtained with a more rational mixture, aluminum hydroxide (Amphojel) and magnesium oxide. Figure 5 presents the titration curves for a glass of sweet milk (200 c.c.) and sweet

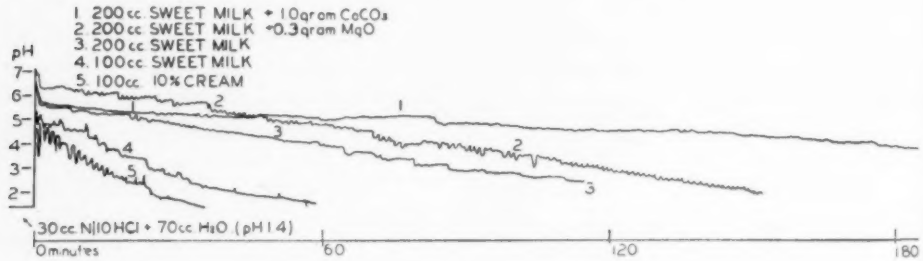

FIG. 5. In vitro.

milk to which calcium carbonate and magnesium oxide have been added. It will be noted that there is an additive effect which produces a long acting antacid and that the high initial pH of calcium carbonate or magnesium oxide alone does not appear, having been effectively buffered by the milk. The tracings for 100 c.c. of sweet milk and 100 c.c. of 10 per cent cream illustrate the better buffering action of the sweet milk. Inspection of the human recordings reveals that the pH changes follow closely the in vitro results. The tracings shown were selected from a total of 66 experiments on 40 subjects.

The subject for figure 6 was T. K., a 40-year-old white male, whose diagnosis was exogenous obesity. He denied any gastrointestinal complaints. In this case histamine .01 mg. per kilogram was used five minutes after the start of each experiment. The two experiments recorded, as in all the in vivo experiments, were done on successive days. It will be noted that al-

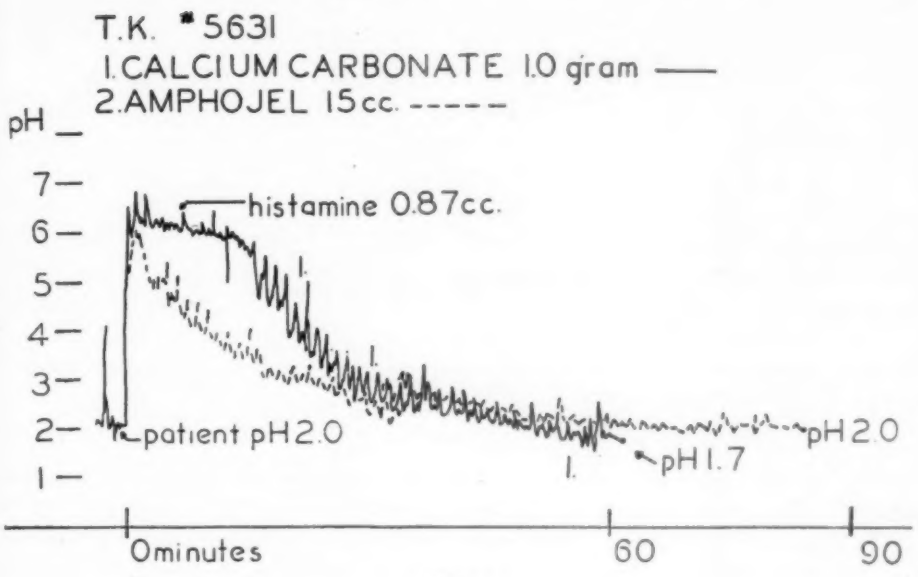

FIG. 6.

though calcium carbonate gives a higher initial pH than an equivalent quantity of aluminum hydroxide in its liquid form (15 c.c. Amphojel, approximately a 6 per cent suspension), the latter has a more sustained action.

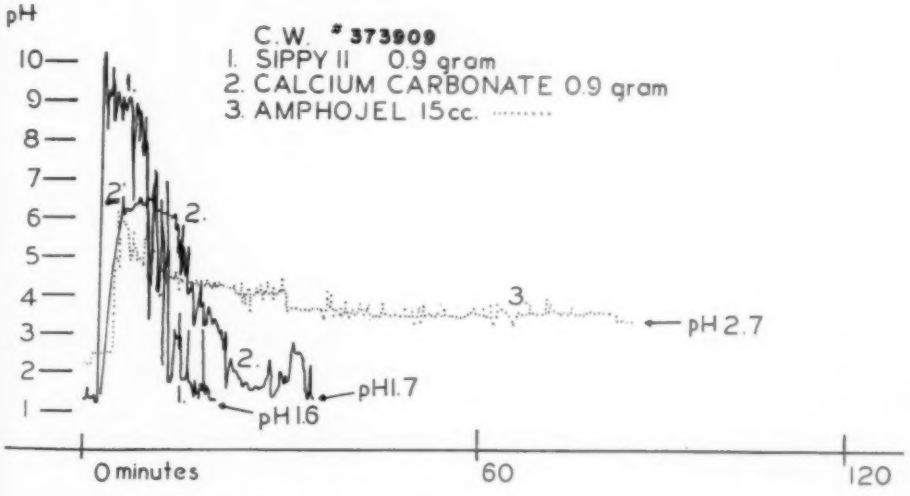

FIG. 7.

C. W., the subject for figure 7, was a 51-year-old white male who had a roentgenological diagnosis of duodenal ulcer. His tracings demonstrate the very high but transient rise of pH in response to 0.9 gm. Sippy II powder (magnesium oxide and sodium bicarbonate in equal quantities). The re-

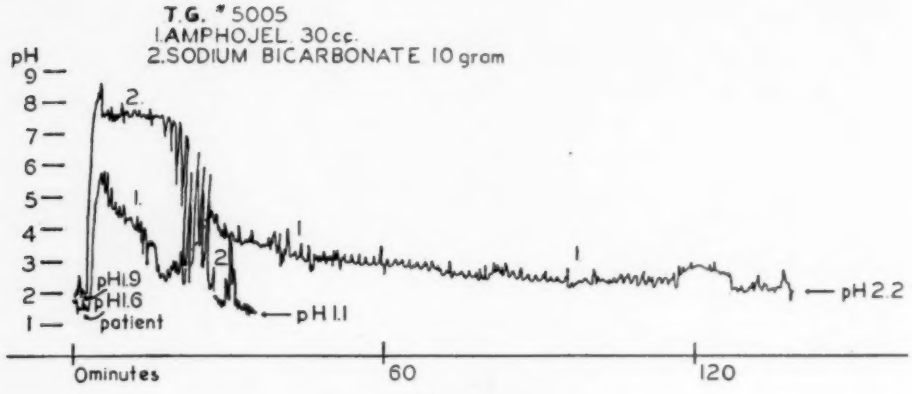

FIG. 8.

sults with calcium carbonate and Amphojel were in the same order as in patient T. K.

In figure 8 the tracings for T. G., a 35-year-old white male who was admitted because of hemorrhage from a gastric ulcer, are shown. They illustrate the high pH achieved with sodium bicarbonate, the rapid exhaustion of its buffering action, and probably the rebound phenomenon (pH 1.0 to 1.1) as contrasted with the sustained action of aluminum hydroxide.

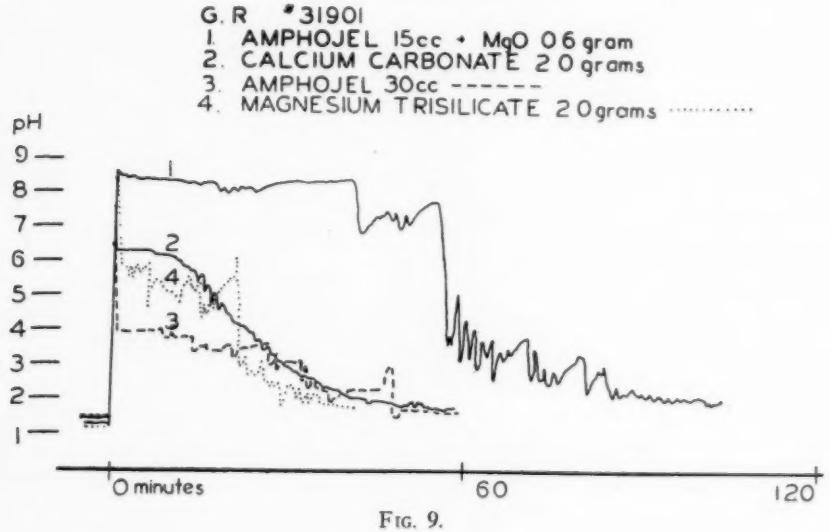

FIG. 9.

The tracings for G. R., a 39-year-old negress (figure 9) with roentgenological evidence of a duodenal ulcer, are illustrative of the prolonged antacid effect of an aluminum hydroxide-magnesium oxide mixture and the reduction of the high pH of magnesium oxide by the buffering action of aluminum hydroxide in such a mixture.

Discussion

The response to environmental [4, 5, 6, 7] factors by different patients becomes relatively constant when each patient is tested repeatedly under the same experimental conditions. Thus, the response of each patient to various antacids is in the same relative order even though there may be a marked absolute variation in the effect of these antacids in different individuals as determined by secretory rate, nature of secretion, emptying time and regurgitation. Our findings in the human being support the previous report [3] that in vitro experiments with the recording glass electrode afford an easy and satisfactory method of obtaining information regarding the antacid properties of various substances.

In addition to the extent of rise in pH and its duration, other factors must be considered in evaluating the efficacy of an antacid. That the human stomach is not normally subjected to high pH values is evident from the work of Bridges and Mattice [8] which showed that over 70 per cent of 2000 representative foods had a pH between 5 and 7. Only three foods had a pH over 8. These findings suggest 7 as the upper limit of the desirable pH range. A rise to 7 or above removes the acid medium which may be necessary to protect the gastric mucosa from the strong proteolytic action of regurgitated trypsin and erepsin which are active in alkaline media. Most investigators feel that the lower effective pH limit is between 5, at which point pepsin is practically inactive, and 3.5, a level at which peptic activity is greatly diminished. Probably more important than peptic activity is the pH level at which pylorospasm is relieved and the vicious circle of pylorospasm, hypersecretion, hypermotility, and ischemia is broken. From the duration of the clinical response this relief may still be present at a pH of 2.5 and a rise above 4.5 never seems to be necessary. The pH rise from a fasting level of 1.5 to a buffered level of 2.5 constitutes an actual reduction to one tenth of the initial hydrogen ion concentration.

Presumably pepsin inactivation is desirable. Mutch [9] has reported its absorption by synthetic magnesium trisilicate and Komerov and Komerov [10] and Schiffrin and Komerov [11] demonstrated the precipitation and inactivation of pepsin in vitro and in vivo in dogs by colloidal aluminum hydroxide. With both substances more complete removal of pepsin was obtained if the free hydrochloric acid was buffered, but adequate pepsin inactivation was obtained without excessive reduction of acidity with aluminum hydroxide.

It is also essential that the antacid does not permanently remove the acidifying effect of gastric contents or the latter will not be available to counteract the alkalinity of the digestive juices present in the small intestine. For example, calcium carbonate (and all antacids which are not amphoteric in nature) yields neutral salts which cannot react with the alkaline intestinal juices, permits the intestinal alkalis to be reabsorbed, and taxes the buffer mechanism of the blood. The absence of this undesirable effect permits

the use of as large a dose as is necessary of amphoteric buffers without danger of systemic alkalosis.

Conclusions

1. Antacids commonly used in ulcer therapy have been evaluated by means of a continuous recording pH meter in vitro and in the human being

2. The similarity of experiments in vitro and in the human stomach recommend the former method as an adequate procedure for analysis of pH changes by various antacids.

3. Magnesium oxide, peroxide, hydroxide, and carbonate are the most effective antacids in a purely chemical sense.

4. These as well as calcium carbonate when combined with milk or colloidal aluminum hydroxide are effectively buffered in their alkaline range and produce long acting antacids.

5. Milk or aluminum hydroxide in adequate dosage best fulfills the physiological criteria of ideal antacids as stated in our discussion.

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SULFONAMIDE THERAPY OF BACTERIAL ENDOCARDITIS; RESULTS IN 42 CASES *

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New Orleans, Louisiana

During the years 1938 to 1941, inclusive, there were 67 cases of bacterial endocarditis among the patients admitted to the Charity Hospital. Forty-two of these cases received therapy with one or more of the sulfonamide drugs. This report, reviewing the 42 cases which received sulfonamide therapy, is made in order to add data to those recorded by numerous authors relating to the effectiveness of the sulfonamide drugs in bacterial endocarditis.

Criteria for Diagnosis. The diagnosis was based either upon (1) a compatible clinical picture plus one or more positive blood cultures, or (2) necropsy evidences. In 32 cases the diagnosis was established ante mortem by the first criterion; in the other 10 cases the presumptive diagnosis of bacterial endocarditis, unestablished during life of the patients by blood culture, was confirmed by postmortem examination. No attempt has been made to differentiate between acute and subacute forms of the disease.

Data Regarding Incidence. The cases were evenly distributed between the sexes and races, there being 12 white males, 10 white females, nine colored males, and 11 colored females. The age range was from two to 75 years, the majority of cases falling between the ages of 15 and 30. The duration of hospital stay varied from two to 202 days, the average stay being about seven weeks.

Sites of Vegetations. Based on postmortem findings in 30 cases, and on clinical data in 12 cases, the sites of vegetations may be listed as follows:

Mitral valve	18 cases
Aortic valve	8 cases
Mitral and aortic valves	7 cases
Tricuspid valve	2 cases
Aortic and tricuspid valves	1 case
Pulmonary valve	1 case
Aortic, mitral, and tricuspid valves	1 case
Congenital defects	4 cases

Bacteriology. In the 32 cases with positive blood cultures, the following organisms were recovered:

Streptococcus viridans	20 cases
Beta hemolytic streptococcus	1 case
Staphylococcus aureus	4 cases
Staphylococcus albus	2 cases
Pneumococcus	3 cases
Streptococcus viridans and pneumococcus	1 case
Eberthella typhi	1 case

In 10 cases positive blood cultures were not obtained.

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From the Departments of Medicine of the Louisiana State University School of Medicine and the Charity Hospital of Louisiana in New Orleans.

Therapy. Sulfanilamide alone was employed in 20 cases; sulfanilamide and sulfapyridine in nine cases; sulfapyridine alone in six cases; sulfapyridine and sulfathiazole in three cases; sulfamethylthiazole in one case; sulfanilamide, sulfapyridine, and sulfathiazole in two cases; and sulfapyridine, sulfathiazole, and sulfadiazine in one case.

There was great variation in the total amounts of sulfonamide drugs given to different patients, but as a rule the dosage per day was large. The total amounts given to individual patients bore a direct relationship to the duration of the hospital stay. Thus the largest total dose, 1043 grams, was given to a patient who spent 202 days in the hospital, and the smallest total dose, two grams, was given to a patient whose hospital stay was but two days. In most cases sulfonamide therapy was continued until death, or until toxic effects of the drugs used necessitated their discontinuance. The successive use of different drugs of the sulfonamide groups in a given patient was always due to failure of the drug used first, or to the occurrence of toxic manifestations due to the first drug used.

Frequent blood transfusions were given to most of the patients. In two patients hyperpyrexia induced by the intravenous injection of typhoid vaccine was used as an adjunct to sulfonamide therapy. Treatment was otherwise supportive and symptomatic.

Results. All of the patients died. In some patients there were temporary remissions in the temperature curve, but for the most part the disease pursued a course apparently unaffected by the treatment.

Necropsy Findings. Autopsy was performed in 30 cases, 71 per cent of the total number. In all these cases characteristic lesions of acute or subacute vegetative endocarditis were found. In no case was there evidence of healing of the lesions. Evidence of embolism was present in 28 cases. The kidneys and spleen were the most frequent sites of infarction, but, in the order of their frequency, infarcts of the brain, lungs, heart, liver, and thyroid were also encountered.

Comment

Nothing is proved by this series of cases regarding the efficacy of the sulfonamide drugs in the treatment of bacterial endocarditis. There is only proof that in these cases the drugs used, in the dosage employed and in the duration of their employment, were without curative effect. It is to be noted that sulfanilamide alone was used in almost half the cases; sulfapyridine, alone or in combination with other drugs, in 21 cases, exactly half of the series; sulfathiazole in only six cases; and sulfadiazine in but one. It should also be noted that this series is unusual in that almost half of the cases were due to organisms other than the *Streptococcus viridans.*

This series, therefore, adds only to the total number of reported cases of bacterial endocarditis in which sulfonamide drugs have been used. Since the cases herein reported are taken from a total number of 67 proved cases

of bacterial endocarditis encountered during a four-year period, additional data regarding the outcome in cases which have not been treated with sulfonamide drugs are furnished by this report. There were 25 such cases observed during the four-year period, and 25 deaths.

Summary

During the four-year period covering the years 1938 to 1941, inclusive, 67 proved cases of bacterial endocarditis were encountered in the Charity Hospital. One or more of the sulfonamide drugs were used in the treatment of 42 cases, and no sulfonamide drugs in 25. All 67 of the patients died.

CLINICAL EVALUATION OF CEDILANID*

By Maurice Sokolow, M.D., and Francis L. Chamberlain, M.D.,
San Francisco, California

The pure glycosides of digitalis have been the subject of many recent pharmacological and clinical investigations. Originally all the studies were purely chemical, but they have assumed clinical importance. The crude whole leaf of *Digitalis purpurea* commonly used in clinical medicine has never been an ideal therapeutic agent. The various preparations differ widely in composition and potency, and require biological standardization. Furthermore, the U.S.P. product may vary in strength with each revision. For instance, the digitalis in U.S.P. XI is approximately 30 per cent more potent than that in U.S.P. X, and the United States Pharmacopeia allows a 40 per cent range between the weakest and the strongest preparation. Gold [1] assayed various commercial products and found a three-fold difference in strength although all were labeled U.S.P. XI. This difference in strength is of great importance when parenteral therapy of digitalis in gravely ill patients is considered or when constant potency is desired for maintenance doses.

Smith [2] and Stoll [3] were the pioneers in the chemical isolation of the pure glycosides of digitalis. Stoll studied both *Digitalis purpurea* and *Digitalis lanata*. A diagram from his monograph illustrates the similarities of, and the differences between the two types of digitalis (chart 1). Each has three glycosides but lanatoside C, the third glycoside of lanata, has no close chemical relationship to the glycosides of purpurea and is not found in the ordinary U.S.P. *Digitalis purpurea*. This glycoside has been isolated in crystalline form and has been standardized by weight. It does not require biological assay.

Early clinical work has centered on lanatoside C because the pharmacologic observations of Moe and Visscher [4] suggested that it was the most potent and the least toxic of the glycosides. The earliest clinical reports which indicated that it was a potent therapeutic agent came from continental investigators. Wayne [5] specifically used digoxin, a breakdown product of lanatoside C, whereas others [6, 7] used lanatoside C. The first American reports were a series of articles by Gold and his co-workers on the pure glycosides.[8, 9, 10] The most extensive clinical study was made by Fahr and La-Due [11] who showed that lanatoside C is potent both orally and intravenously and that the speed of action of the intravenous product resembles that of strophanthin. Our study of lanatoside C was begun independently two years

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From the Department of Medicine, University of California Medical School, San Francisco.
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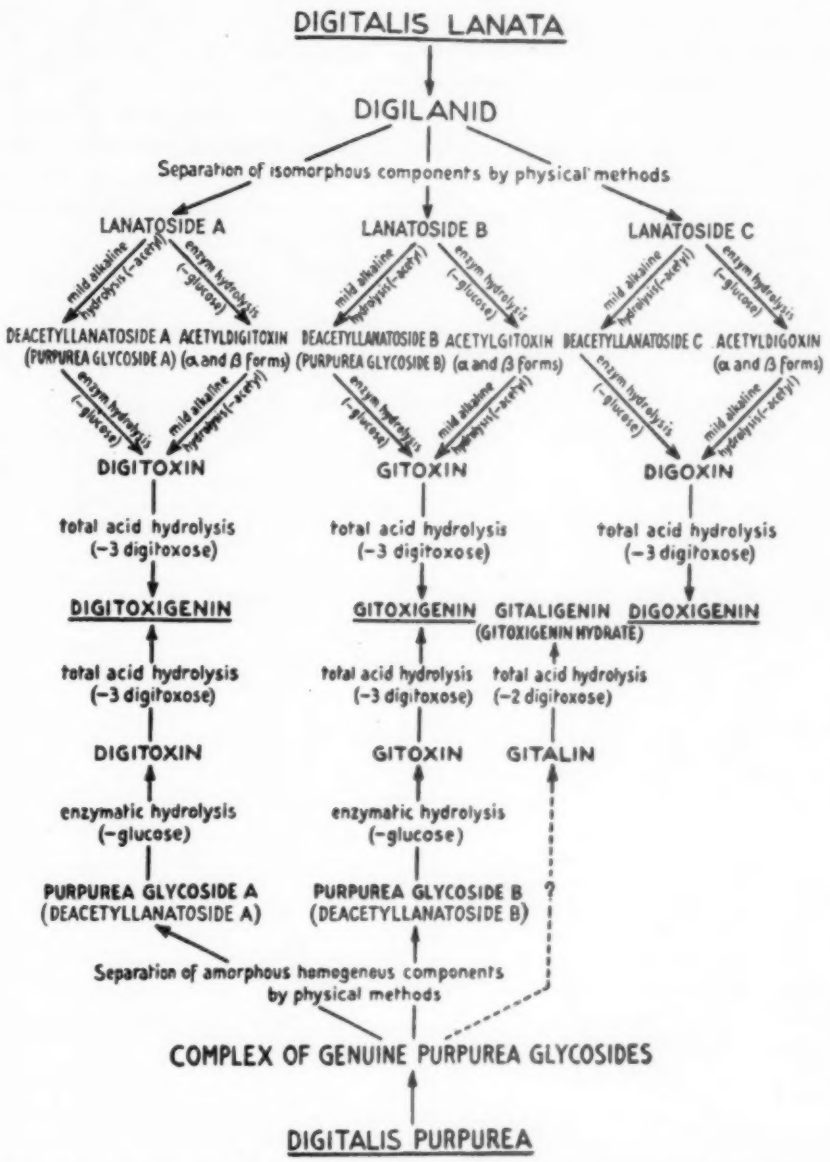

CHART 1. The newly discovered relationships between the lanata and purpurea glycosides (after Stoll and Kreis).

ago, and confirms and extends some of the observations made by Fahr and LaDue.

In interpreting the dosage of lanatoside C, it is important to note, as was first emphasized by Gold,[8] that dosage and toxicity of the pure crystalline glycosides cannot be deduced from comparative values obtained on test animals but must be determined clinically in man. The dosage must be con-

sidered in terms of milligrams and not of cat units. In man, one cat unit of digitalis leaf may produce the same clinical effects as five cat units of lanatoside C when both are given orally.

Lanatoside C (or Cedilanid) is marketed by the Sandoz Chemical Works, Incorporated. The oral preparation is made in tablets of 0.5 mg. each and the intravenous preparation in ampoules, each cubic centimeter of which contains 0.20 mg. of the drug. A cat unit is considered equivalent to 0.28 mg.

Method of Study

The patients who were chosen for the investigation presented the usual indications for digitalis therapy, such as congestive failure, paroxysmal

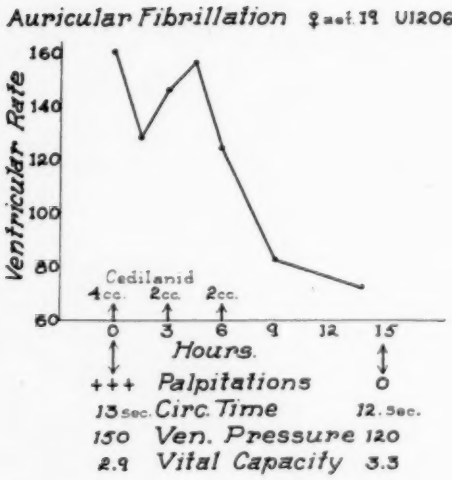

Fig. 1.

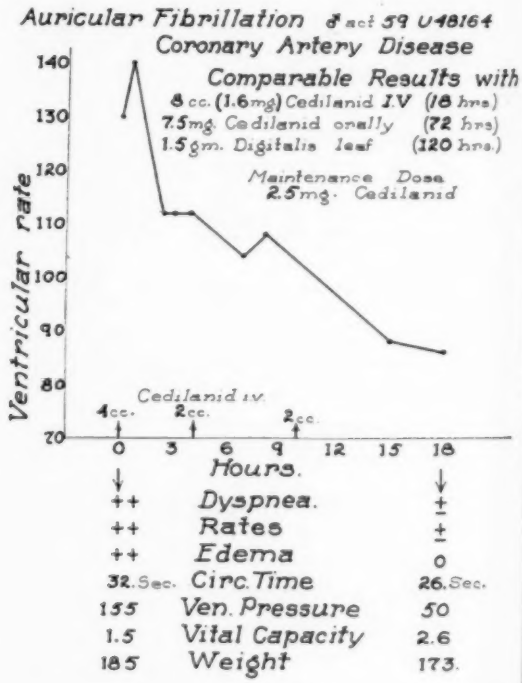

Fig. 2.

nocturnal dyspnea, auricular fibrillation and auricular flutter. Most of them were hospitalized. Cedilanid was given orally or intravenously after a preliminary control period of rest in bed, restriction of salt and fluids, and sedation. In many instances repeated determinations of the venous pressure,* circulation time,† and vital capacity were made to supplement the usual clinical observations of changes in dyspnea, orthopnea, cyanosis, venous engorgement, râles, cardiac rate, blood pressure, size of liver, peripheral edema,

* Venous pressure was determined by the direct method with a spinal fluid manometer.

† Circulation rates were determined with the objective alpha lobeline (Sandoz) method by injecting from 0.003 to 0.005 gm.

weight and fluid balance. These data were recorded on mimeographed charts. Repeated electrocardiograms were taken during and after digitalization in order to determine the effects on the electrocardiogram and on the rate of excretion.

The dosage of cedilanid (see Dosage, page 208) varied according to the speed desired for digitalization. The maintenance dose for both oral and

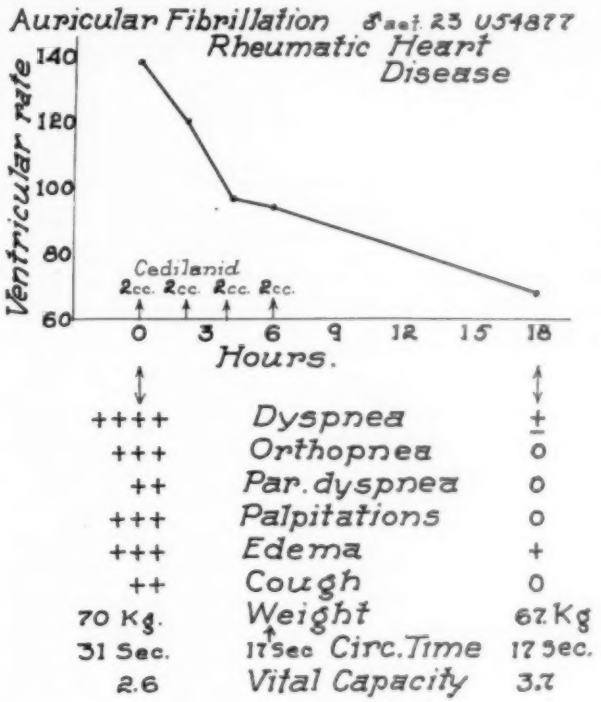

FIG. 3.

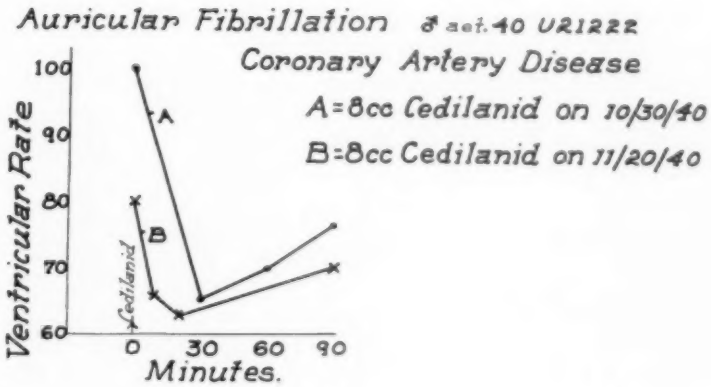

FIG. 4.

intravenous preparations was obtained by frequent examination of each patient over periods of months. All observations were made after the patient had been recumbent for at least 20 minutes. The maintenance dose was considered the dose just short of the point of mild toxic symptoms which could be maintained for at least a month.

Many of the patients had been previously digitalized and maintained with *Digitalis purpurea*. Some were subsequently digitalized with purpurea if failure occurred when cedilanid was omitted. In this way a comparison of the dosage, toxicity, and excretion of *Digitalis purpurea* and cedilanid was possible.

Clinical Results

The therapeutic results with cedilanid paralleled the best previously obtained with *Digitalis purpurea*. Of 95 patients, approximately 40 per cent had cardiac failure with sinus rhythm. All but three of these received striking therapeutic benefits. They had varying degrees of failure, but the almost uniform improvement in dyspnea, orthopnea, edema and other symptoms confirms the many observations made in recent years which prove the value of digitalis in cardiac failure with sinus rhythm.

Approximately one-third of the patients had auricular fibrillation with or without failure, and all showed definite improvement. The speed of action of the drug when given intravenously was particularly noteworthy.

Auricular flutter was present in 17 instances. After administration of cedilanid, conversion to auricular fibrillation occurred in two and to sinus rhythm in 14 patients; one converted spontaneously. Frequently the conversion took place within 24 hours. The dose was the same as that given in failure. Representative charts are shown in figures 6, 7 and 8.

Dosage

At first the dose was determined by trial and error. When our investigation was begun, the only clinical reports were those of continental investigators. We found that their dosage was too low and that our figures came close to those of Fahr and LaDue.[11]

The *oral* digitalizing dose was determined accurately in 45 patients. It varied from 7 mg. in 24 hours to 16 mg. in 96 hours; the average dose was 7.5 mg. in 72 hours. The range of dosage is given in table 1.

Table 1

No. of Hours	No. of Cases	Dose mg.
24	9	4–7
48	6	5–14
72	15	5–9
96	5	6–16
>96	9	9–16

The *intravenous* cedilanid was given in full dosage to 41 patients. Digitalization was accomplished by single or multiple injections within 24 to 48 hours. The digitalizing dose varied from 6 to 16 c.c. (1.2 to 3.2 mg.) in 24 hours. No patient had even mild toxicity on less than 8 c.c. (1.6 mg.) in 24 hours. Three patients had mild transient nausea when 8 c.c. were given in a single dose. Several patients received 2 c.c. (0.4 mg.) every four hours for three to four days until full digitalization occurred. No toxic symptoms were observed and the clinical results were excellent.

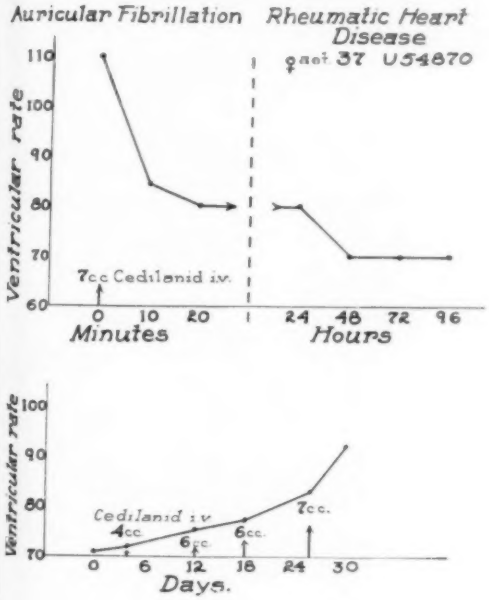

FIG. 5.

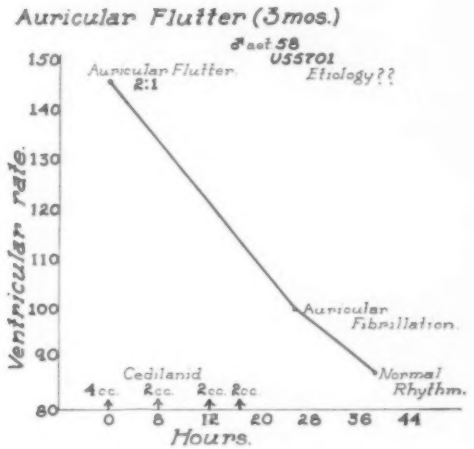

FIG. 6.

Striking clinical effects were obtained with the intravenous preparation. An abrupt drop in ventricular rate frequently occurred within 10 minutes (figures 4 and 5), although the full effect usually required an hour. This confirms the observations of Fahr and LaDue.[11] In some patients the effect on the ventricular rate was not obtained until the digitalizing dose had been reached. In figure 1 it is seen that the third dose of 2 c.c. produced an abrupt and sustained fall in ventricular rate, whereas 6 c.c. previously administered had had only a partial and unsustained effect. In many instances the patient entered the hospital in desperate cardiac failure and within 24 hours showed striking subjective and objective improvement. Typical examples are shown in figures 2 and 3.

For intravenous administration of cedilanid we have found that the procedure of choice is an initial dose of 6 c.c. (1.2 mg.) followed by doses of 2 c.c. (0.5 mg.) every three to four hours until the desired beneficial or mild toxic symptoms are obtained.

The *maintenance* dose of oral cedilanid was determined accurately in 47 patients. For a period ranging from several months to two years, these patients were seen every two to four weeks and the clinical state and resting ventricular rates after administration of varying amounts of the drug were noted. The dose needed for maintenance ranged from 0.5 to 2.5 mg. The average maintenance dose was 1.6 mg.

The maintenance dose of the intravenous preparation was determined in three patients. It was 1.0 c.c., 1.2 c.c., and 2.0 c.c. respectively, or an average of 0.34 mg. daily. Figure 5 illustrates the method of determining the maintenance dose. The patient received 23 c.c. over a period of a month during which time the ventricular rate gradually escaped from 70 to 90; the maintenance dose, therefore, was greater than 1.0 c.c.

Comparison of Oral and Intravenous Cedilanid

Accurate comparison of the digitalizing dose of the oral and intravenous preparations of cedilanid in the same patient on different occasions was made in seven patients. Table 2 illustrates the results. The average oral-intra-

Table II

Oral Dose (72 hours) mg.	Intravenous Dose Oral/Intravenous	
	(24 hours) mg.	Ratio
7.5	1.6	4.7
9.0	2.1	4.3
7.5	1.4	5.3
7.0	1.2	5.8
6.4	1.6	4.0
7.0	1.9	3.7
9.0	1.6	5.6

venous ratio is 4.8 to 1. Thus, in terms of milligrams, 4.8 times as much drug is required for oral as for intravenous digitalization. However, if we assume an average maintenance dose of 1.6 mg. and correct the oral digitalizing dose to that obtained in 24 hours, the ratio is 4.4 to 1.6, or 2.75. Thus, in terms of 24-hour digitalization, 2.75 times as much drug is required for the oral as for the intravenous dose.

No significant difference in the clinical effectiveness of the oral and intravenous preparations could be determined, except with regard to the speed of effect. Only mild toxic symptoms were obtained with the intravenous drug whereas with the oral drug they were more severe. Further work is in progress to determine whether the effects are more constant and predictable if the drug is given intravenously. It may be the more uniform because the individual variations in absorption need not be considered.

The intravenous product is not desirable for maintenance because of its rapid excretion and the necessity for continued and frequent injections.

Duration of Effect

Approximately two to three weeks are required for subsidence of the electrocardiographic abnormalities produced by cedilanid. Re-escape of the ventricular rate in auricular fibrillation may occur in seven to eight days; the exact time was determined in only six hospitalized patients. Wide oscillations in ventricular rate for 24 to 36 hours frequently precede the fixed acceleration noted with escape. The diurnal oscillations in a well controlled ventricular rate are small. The P–R prolongation frequently disappears in three to four days. Slight residual electrocardiographic abnormalities were occasionally seen three to four weeks after the drug had been discontinued.

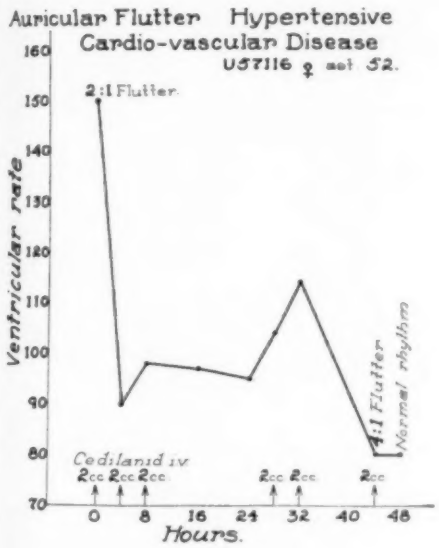

Fig. 7.

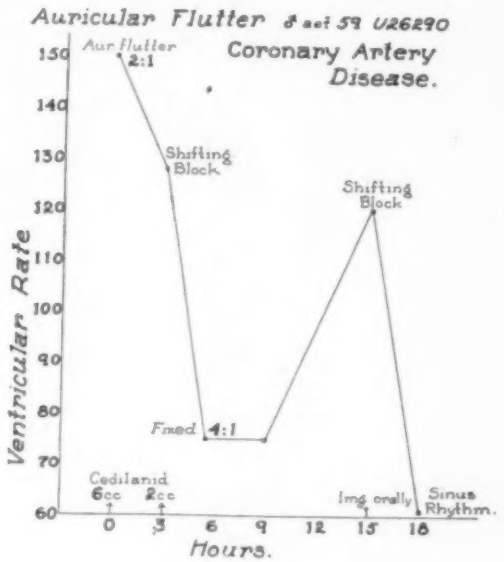

Fig. 8.

Comparison of Cedilanid and Digitalis Purpurea

No significant objective difference could be seen in the effect of the oral preparations. In patients who considered either one or the other drug as superior, no significant differences could be demonstrated. Patients who failed to respond to one of the drugs did not respond to the other. Figure 9 illustrates the effects in a patient with auricular flutter who was treated with both drugs during different attacks. Patients saturated with either of the two drugs could be maintained on the other drug. These effects were observed in 44 patients.

In 21 patients accurate data on the comparative maintenance doses of cedilanid and *Digitalis purpurea* were obtained. The average maintenance doses were 1.6 mg. and 0.13 gm. respectively. This in terms of cat units is

a ratio of 5 to 1; but, as noted previously, cat units can not be used to compare crystalline and crude substances.

Accurate data on the comparative digitalizing dose of the two drugs were obtained in 10 patients. The average digitalizing dose in 72 hours was 7.6 mg. for cedilanid and 1.5 gm. for *Digitalis purpurea*. This, in terms of cat units, is a ratio of 2 to 1.

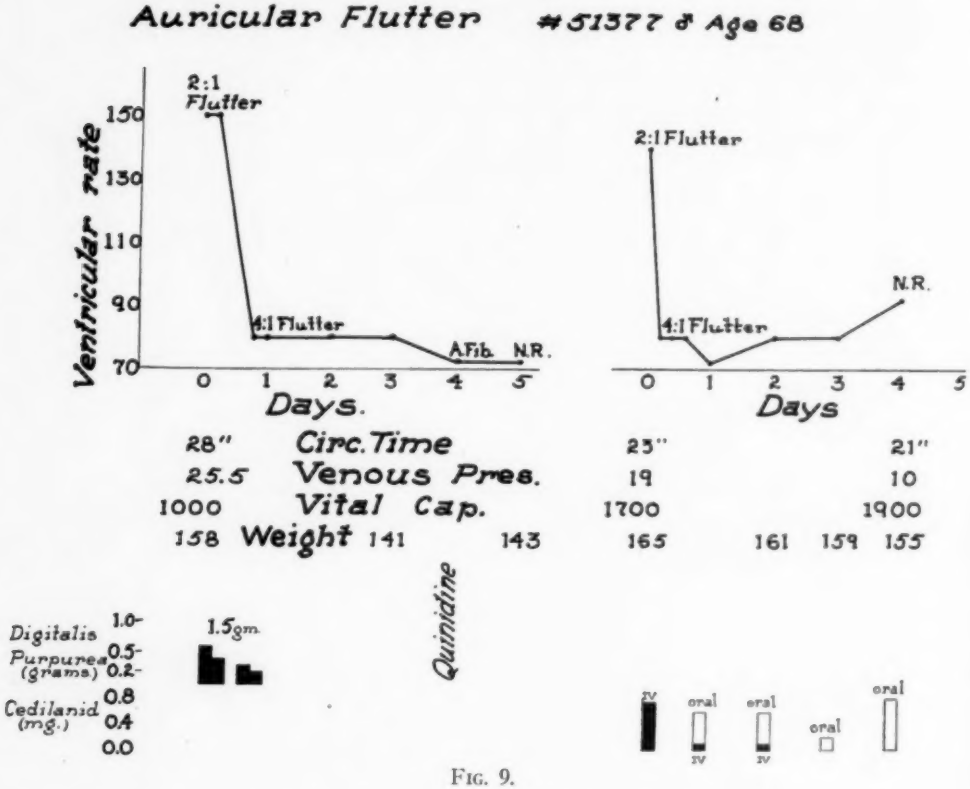

FIG. 9.

It is of interest to note that the digitalizing-maintenance ratio of cedilanid is 7.6 to 1.6, or 4.7, whereas that of *Digitalis purpurea* is 1.5 to 0.13, or 11.3. Thus, the maintenance dose of cedilanid is approximately one-fourth the digitalizing dose whereas the maintenance dose of *Digitalis purpurea* is one-eleventh the digitalizing dose. Therefore, it is apparent that oral cedilanid is absorbed or utilized roughly three times as easily as is oral *Digitalis purpurea*. If, as Gold [1] has stated, only 10 to 20 per cent of *Digitalis purpurea* is absorbed from the gastrointestinal tract, then 30 to 60 per cent of cedilanid is absorbed. These figures compare favorably with the doses required to digitalize one patient with both oral and intravenous cedilanid (figure 2).

According to our clinical study, the most obvious benefit of cedilanid is derived from its intravenous use in urgent cardiac failure or when rapid, ac-

curate dosage is desired. Its uniform potency and its purity allow greater confidence in giving large intravenous doses. The increased absorption of oral cedilanid may prove important.

Summary

1. Lanatoside C (cedilanid) is a pure, stable, crystalline glycoside derived from *Digitalis lanata*.

2. It is a potent therapeutic agent in congestive cardiac failure with normal rhythm, in auricular fibrillation and in auricular flutter.

3. In auricular fibrillation, intravenous cedilanid produces an abrupt fall in the ventricular rate, frequently within 10 minutes.

4. The average oral digitalizing dose of cedilanid is 7.5 mg. in three days.

5. The average intravenous digitalizing dose is 8 c.c. (1.6 mg.) in 24 hours.

6. The average maintenance dose of oral cedilanid is 1.6 mg.

7. Oral cedilanid apparently is absorbed three times as readily as oral *Digitalis purpurea*. This is based on the fact that the digitalizing dose of cedilanid is only 4.7 times its maintenance dose whereas the digitalizing dose of *Digitalis purpurea* is 11.3 times its maintenance dose.

8. No striking difference in clinical effects was noted between oral cedilanid and oral *Digitalis purpurea*.

9. The most important therapeutic advantage of cedilanid is obtained from the intravenous preparation, primarily because of its rapid action.

10. Approximately 2.8 times as much drug is required for oral as for intravenous 24-hour digitalization.

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PANCREATIC TISSUE EXTRACT (INSULIN-FREE) IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE *

By Charles Klein, M.D., Gamliel Saland, M.D., F.A.C.P., and Herman Zurrow, M.D., *Bronx, New York*

It has become the custom, in the literature on peripheral vascular disease, to state that there has been an upsurge of interest in, and an increase in clinical and physiological understanding of this type of disorder in recent years. To those who work intensively in this field, however, it is evident that therapeutics has not kept pace with diagnosis. Moreover, the problem of treatment becomes progressively more important as our increasing understanding of peripheral vascular diseases uncovers more cases, and as our population shifts into the age group in which vascular disease is one of the commoner causes of disability.

It is our purpose, in this paper, not to introduce a new therapeutic agent, but to present the results of a three-year study of one of the first substances used in the treatment of peripheral vascular disease, namely, insulin-free pancreatic tissue extract. This substance has been used for at least 10 years. Acknowledgment for its introduction is generally accorded to Frey and Kraut.[1] It has been used extensively in Europe for the treatment of angina pectoris as well as of claudication. Wolffe has contributed to our understanding of its chemical nature and physiologic action,[2] and he has submitted several reports concerning the clinical evaluation of its effects.[3, 4] Recently, Fisher, Duryee, and Wright described a partly objective method for evaluating the effect of therapeutic agents on claudication time and submitted a favorable report on the action of insulin-free, pancreatic tissue extract.[5]

At our Clinic, the study of pancreatic tissue extract † was divided into three parts: (1) Observation of the "immediate" effect, i.e., within three hours, of intramuscular injection of the tissue extract on superficial (skin) and deep (muscle) temperature. (2) Observation of the "immediate" effect, i.e., within one-half hour, of intramuscular injection of the tissue extract on claudication time, as measured by the ergometer. (3) Evaluation clinically, according to criteria set forth by us [6] and outlined below, of the effect of prolonged, regular administration of pancreatic tissue extract by intramuscular injection, for periods varying from six to 24 months.

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† In our studies, three different commercial brands of pancreatic tissue extract were used. The extract designated hereafter as No. 1 is Tissue Extract No. 568 (Sharp & Dohme); that designated No. 2 is Pancreatic Hormone (Grant); No. 3 is Depropanex (Sharp & Dohme). We wish to express our appreciation to these companies for their kindness and courtesy in supplying our Clinic with these materials for clinical study.

1. *Effect on Skin and Muscle Temperature.* The effect of deproteinated, insulin-free, pancreatic tissue extract (Depropanex) on the skin surface temperature of the great toe and on the calf muscle temperature was studied in nine patients. At the start of each study the patient was permitted to rest, lying on a table, with the lower extremities exposed to room temperature, which was between 21 and 26° Centigrade. An intramuscular thermocouple needle was inserted into the calf muscles of one extremity and connected with a galvanometer adjusted to give temperature readings in degrees Centigrade.* A skin thermocouple † was used to measure skin surface temperature; the area of skin on the dorsum of the great toe just below the nail base was used. Frequent preliminary readings were taken. When the skin and muscle temperatures appeared stable after at least two consecutive readings 10 minutes apart, the study was begun on the patient. One-half to one hour was usually required before temperatures no longer varied. Room temperatures were recorded, and care was taken to keep them as constant as possible. Rectal temperatures were taken before any procedure was started, and the study not done if the reading was higher than 99.8° F. Three cubic centimeters of pancreatic tissue extract were injected intramuscularly, and skin surface and muscle temperatures were recorded at approximately 15-minute intervals for from two to three hours.

The nine patients studied were taken from the Peripheral Vascular Disease Clinic. They had never been treated with pancreatic tissue extract. They all had had a complete medical and peripheral vascular workup. They consisted of two normal patients and seven patients with arteriosclerosis obliterans.

In the interpretation of results, it was considered that skin temperature changes of less than 1° Centigrade were not significant, being well within the range of technical error. Changes in surrounding environmental temperature were taken into consideration in analyzing results, as indicated below.

Results (see table 1): In eight cases, the muscle temperature fell from 0.5 to 4.1° Centigrade within two hours after the injection of pancreatic tissue extract. These eight included the two normal patients. In one case of arteriosclerosis obliterans there was a rise of 1.0°; however, in this study, the room temperature rose 3°.

In five cases, the skin surface temperature was not appreciably altered. In one case, there was a rise in temperature of the right and left great toes of 2.2 and 2.1°, respectively. This was a case of arteriosclerosis obliterans. In one case, without peripheral vascular disease, there was a rise in skin temperature of 1.0° in the left great toe. In one case of arteriosclerosis obliterans there was a drop of 3.4° in the right great toe, a drop of 2.7° in the left great toe. In another case of arteriosclerosis obliterans there was a drop of 2.7° in the right great toe, and a drop of 3.3° in the left great toe.

* Leeds-Northrup Instrument Co.
† Taylor Dermatherm.

TABLE I

Effect of Pancreatic Tissue Extract on Skin and Muscle Temperature

Patient and Diagnosis	Skin Temperature Right Great Toe		Skin Temperature Left Great Toe		Deep Muscle Temp.: Rt. Calf	
	Before Injection	2 Hours After Inj.	Before Injection	2 Hours After Inj.	Before Injection	2 Hours After Ini.
S. F., Arteriosclerosis obliterans	27.4	26.9	24.0	23.6	34.5	30.7
M. B., A.S.O.	27.3	24.0	27.4	24.7	32.2	30.0
J. S., A.S.O.	26.3	28.5	26.3	28.4	33.8	33.0
A. K., A.S.O.	21.4	21.9	20.2	20.8	33.6	29.5
J. P., no vascular disease	23.0	23.5	22.5	23.5	36.4	35.9
M. K., A.S.O.	22.5	22.5	22.3	22.5	34.5	33.6
M. S., A.S.O.	25.9	26.1	24.6	25.1	34.1	35.2
R. S., no vascular disease	22.1	22.2	22.1	21.7	36.3	33.1
C. W., A.S.O.	28.6	25.9	28.3	24.8	33.4	32.0

Summary: Of nine patients studied, a drop in muscle temperature occurred in eight cases, a slight rise in one case, within two hours after the intramuscular injection of 3 c.c. of pancreatic tissue extract. In five cases there was no significant alteration in skin surface temperature, a drop in two cases, a slight rise in two cases.

2. *"Immediate" Effect on Claudication Time.* Nine patients, all suffering from arteriosclerosis obliterans, were used in this study. Four could walk no more than one-half to one city block without the occurrence of calf muscle pain severe enough to require cessation of walking. Four could walk about one and one-half city blocks before the onset of claudication pain. One patient could walk 15 blocks.

Depropanex (Sharp & Dohme) was the tissue extract used, and normal saline was used as a control substance in the control studies. Measurement of the claudication time was done by means of an ergometer. This consisted, essentially, of a 10 pound weight connected with a foot pedal by means of a thin chain passing over a pulley. The patient raised this 10 pound weight six inches by depressing the pedal with his foot; by keeping the heel fixed as much as possible, this threw the greatest part of the work on the calf muscles.

The procedure used was as follows: The patient was seated before the ergometer, at rest, for one-half hour. Then, using the limb showing the greater involvement, the patient depressed the foot pedal at a fixed, regular rate until muscle pain set in. This interval was timed, and the number of times the foot pedal had been depressed in this period was read from the counter. Another half-hour rest period was given, and the ergometry was repeated. Then 3 c.c. of pancreatic tissue extract were injected intramuscularly, a half-hour rest period was given, and the ergometry was again repeated. One week later the above procedure was repeated in its entirety, with the same patient, using the same limb, except that 3 c.c. of normal saline were injected in place of the pancreatic tissue extract.

Results (see table 2): After Depropanex injection, three patients showed

TABLE II

Effect of Tissue Extract (Depropanex) on Claudication Time of 9 Patients Suffering from Arteriosclerosis Obliterans. *Ergometric Measurements*

Case No.	"Clinical" Claudication Distance		Depropanex			Normal Saline		
			After 1st ½-Hour Rest Period	After 2nd ½-Hour Rest Period	½-Hour After Tiss. Ext. Injection	After 1st ½-Hour Rest Period	After 2nd ½-Hour Rest Period	½-Hour After Saline Injection
65122	1½ blocks	Secs.	186	211	254	162	289	282
		Strokes	228	253	360	177	277	305
109181	1½ blocks	Secs.	121	83	113	132	113	229
		Strokes	121	96	126	142	121	314
74797	1½ blocks	Secs.	261	—	209	over 12 minutes		
		Strokes	276	—	245	—	—	—
82293	1½ blocks	Secs.	21	84	60	42	61	120
		Strokes	7	10	33	41	71	100
114246	½ block	Secs.	130	143	93	146	143	233
		Strokes	148	164	111	167	168	282
84081	½ block	Secs.	187	154	140	199	201	146
		Strokes	167	167	156	235	285	177
87815	Less than ½ block	Secs.	72	63	73	75	99	93
		Strokes	84	74	84	96	135	121
73005	15 blocks	Secs.	95	59	115	not reported		
		Strokes	114	75	121			
116374	½ block	Secs.	51	58	37	24	29	28
		Strokes	58	70	36	—	—	—

a significant prolongation of claudication time (43, 33, 56 seconds, and 107, 30, 46 pedal strokes, respectively); four patients showed a decrease in claudication time (52, 50, 14, 21 seconds and 31, 53, 11, 34 pedal strokes, respectively); one patient showed practically no change (10 seconds, 10 strokes more); one patient did not adhere to the rate and rhythm set, and pedalled 23 strokes more but 24 seconds less.

After normal saline (control) injection, three patients showed an increase in claudication time (116, 59, 90 seconds and 193, 29, 114 pedal strokes, respectively); one patient showed a 7-second decrease, but could pedal 28 times more; one patient showed only a 1-second difference, with pedal strokes not reported; two patients showed a decrease of claudication time (6, 65 seconds and 14, 108 pedal strokes, respectively); two cases were not reported.

In summary, it could be stated that pancreatic tissue extract (Depropanex) had no specific effect in prolonging claudication time within one-half hour of injection, as measured by ergometer.

3. *Clinical Evaluation of Effect of Prolonged Administration of Pancreatic Tissue Extract.* Thirty-nine patients were used as subjects. Of

these, 15 were used as controls; they were given normal saline, 3 c.c. intramuscularly, or were given no injections of any kind, and simply reported at stated intervals for reëxamination and advice. The remaining 24 patients were given pancreatic tissue extract; they were divided into three groups, containing nine, nine, and six patients, respectively. Each one of these groups received a different commercial brand of pancreatic tissue extract. This was given twice a week, in 3 c.c. doses, intramuscularly. Patients in both divisions, tissue extract treated and control cases, were given detailed instruction sheets on care of the feet, diet, use of tobacco, and exercise; they received local foot care and treatment at the Clinic and, from time to time, as the need arose, were given analgesics or sedatives for rest pain.

On admission of the patient to the Clinic, a complete history was taken, physical examination was done, and routine and indicated laboratory tests were performed. The peripheral vascular status of the patient was then determined according to the following scheme[6]:

(*a*) Vascular anatomic status: This was determined by palpation of pulses, by oscillometry, by noting temperature of extremities to touch, by determining degree of rubor on dependency, and of pallor on elevation of the limbs, and by roentgenograms of the extremities for calcification. This factor was then graded from 4-plus bilateral (severest) involvement down through 1-plus unilateral involvement (minimal changes in one limb) to 0 (no evidence of pathologic change in the blood vessels).

(*b*) Tissue anatomic status: This was determined by noting the degree of involvement of deep and superficial tissues, and was graded as follows: 4-plus, gangrene, pregangrene; 3-plus, ulceration; 2-plus, infection (cellulitis, lymphangitis) without gangrene; 1-plus, skin and muscle atrophy, dermatophytosis, nail disturbances, etc.; 0, no apparent tissue changes.

(*c*) Rest pain: The patient was questioned regarding the occurrence of pain, sensations of coldness or burning, or cramping in the extremities when at rest or at night. This, if present, was recorded and graded according to intensity, from 1-plus to 4-plus.

(*d*) Claudication: The patient was asked how many city blocks he could walk before pain in the lower extremity set in which required that he stop and rest. This was graded as follows: 4-plus, if the patient could walk no more than one-half block; 3-plus, if he could walk one-half block to two blocks; 2-plus, two to four blocks; 1-plus, more than four blocks, but still limited; 0, no claudication.

(*e*) Vascular reserve, or capacity for vasodilatation: This was determined by means of the thermal reflex vasodilatation test.[7] Where thermal test did not produce full dilatation, nerve block was performed, wherever feasible. The posterior tibial and common peroneal nerves were infiltrated with 1 to 2 per cent novocaine. Vascular reserve was graded thus: Full dilatation, or rise in skin surface temperature of dorsum of great toe to 30.5° C., was marked 4-plus. A 75 per cent rise from the initial temperature

to 30.5°, 3-plus; a 50 per cent rise, 2-plus; a 25 per cent rise, 1-plus; no rise, or insignificant rise, 0.

(*f*) Functional classification: This represented a summation of the entire disease picture, and can be explained as follows: Class I, patients who have organic vascular disease without symptoms; class II, patients who have organic vascular disease (*a*) with minimal symptoms and (*b*) with moderate symptoms; class III, patients who have organic vascular disease and who are bedridden because of severe pain occurring even at rest, or because of gangrene, ulceration, or infection; class IV, patients who have symptoms of vascular disease without organic vascular disease; this last is the "functional" group.

Every six months the patients in this study were given a complete workup, the previously-described grading procedure was repeated, and the results were charted for comparison.

To show the clinical comparability of the control and the pancreatic tissue extract treated cases, it might be well, at this point, to append the following chart (table 3). It indicates the status of all the patients in our

TABLE III

Description of Patients Used in Study of Effect of Prolonged Administration of Pancreatic Tissue Extract

	Tissue Ext. No. 1	Tissue Ext. No. 2	Tissue Ext. No. 3	Total T.E.	Control Cases
Number of Patients	9	9	6	24	15
Sex of Patients	M: 7, F: 2	M: 8, F: 1	M: 6, F: 0	M: 22, F: 3	M: 14, F: 1
Age Distribution:					
40 to 49	0	2	0	2	1
50 to 59	0	1	0	1	3
60 to 69	6	5	5	16	9
70 to 79	1	1	1	3	1
Etiology:					
Arteriosclerosis obliterans (A.S.O.):	8	4	4	16	10
A.S.O. and diabetes:	0	2	0	2	1
A.S.O. and hypertension:	1	1	1	3	2
A.S.O., diab., hypertens.:	0	0	0	0	1
A.S.O. and C.N.S. syphilis	0	1	0	1	0
A.S.O. and late latent lues:	0	0	1	1	0
Thromboangiitis oblit.:	0	0	0	0	1
Thrombophlebitis with vasospasm:	0	1	0	1	0
Vascular anatomic status: (See text) (B Bilateral; U Unilateral)					
4 + B	2	4	3	9	5
3 + B	1	1	1	3	4
2 + B	1	1	1	3	4
1 + B	2	2	0	4	1
4 + U	0	0	0	0	0
3 + U	1	1	0	2	0
2 + U	1	0	0	1	0
1 + U	1	0	0	1	0
0	0	0	1	1	1

TABLE III (*Continued*)

	Tissue Ext. No. 1	Tissue Ext. No. 2	Tissue Ext. No. 3	Total T.E.	Control Cases
Tissue anatomic status (See text):					
4 +	1	0	0	1	0
3 +	1	1	1	3	0
2 +	1	0	0	1	2
1 +	2	2	2	6	5
0	4	6	3	13	8
Rest pain (See text):					
4 +	0	0	0	0	0
3 +	1	1	0	2	0
2 +	3	2	2	7	1
1 +	0	2	0	2	2
0	4	4	4	12	12
Claudication (See text):					
4 +	2	3	2	7	4
3 +	5	4	2	11	6
2 +	0	2	0	2	1
1 +	0	0	2	2	2
0	1	0	0	1	0
Vascular reserve (See text):					
4 +	0	4	2	6	4
3 +	2	1	2	5	3
2 +	4	1	1	6	0
1 +	1	3	0	4	2
0	2	0	1	3	6
Functional classification (See text):					
I.	0	0	0	0	0
IIa.	3	1	2	6	3
IIb.	3	6	3	12	9
III.	3	1	1	5	2
IV.	0	1	0	1	1

series at the start of this investigation. It can be seen that, though the patients were not selected, they fit into the gradings in each category in such a manner that the percentages of control versus treated cases follow a similar distribution curve in each of the various categories. It should also be noted that all our patients were of the outpatient type, i.e., ambulatory, at the start of our investigation.

Results: These (see tables 4, 5, 6) are grouped according to our findings after 6-, 12-, and 18-month periods of treatment, and are tabulated in the pattern of classification described above. Because there was no significant difference in the results obtained with the three different commercial brands of pancreatic tissue extract and because the individual figures for each brand are too small, all the results for the tissue extract treated cases are reported together.

After six months of treatment, of the pancreatic tissue extract treated cases, two out of nine (22.2 per cent) showed improvement in vascular anatomic status, two out of seven (28.5 per cent) improvement in tissue anatomic status, three out of nine (33.3 per cent) improvement in rest pain,

TABLE IV

Results of Treatment with Pancreatic Tissue Extract. *After Six Months*

Aspect	No. of Patients	Number Improved	Number Same	Number Worse	% Improved
Vascular anatomic status:					
Controls	7	4	2	1	57.1
Tiss. Extr.	9	2	5	2	22.2
Tissue anatomic status:					
Controls	4	1	2	1	25.0
Tiss. Extr.	7	2	4	1	28.5
Rest Pain:					
Controls	7	0	4	3	0.0
Tiss. Extr.	9	3	5	1	33.3
Claudication:					
Controls	6	0	5	1	0.0
Tiss. Extr.	9	6	3	0	66.7
Vascular reserve:					
Controls	7	3	1	3	42.9
Tiss. Extr.	20	8	7	5	40.0
Functional class:					
Controls	7	2	5	0	28.5
Tiss. Extr.	10	4	5	1	40.0

TABLE V

Results of Treatment with Pancreatic Tissue Extract. *After Twelve Months*

Aspect	No. of Patients	Number Improved	Number Same	Number Worse	% Improved
Vascular anatomic status:					
Controls	9	2	3	4	22.2
Tiss. Extr.	15	3	6	6	20.0
Tissue anatomic status:					
Controls	6	0	3	3	0.0
Tiss. Extr.	14	5	6	3	35.7
Rest pain:					
Controls	7	0	4	3	0.0
Tiss. Extr.	14	6	7	1	42.9
Claudication:					
Controls	8	2	4	2	25.0
Tiss. Extr.	15	10	3	2	66.7
Vascular reserve:					
Controls	6	3	1	2	50.0
Tiss. Extr.	15	3	4	8	20.0
Functional class:					
Controls	8	2	4	2	25.0
Tiss. Extr.	15	9	3	3	60.0

TABLE VI

Results of Treatment with Pancreatic Tissue Extract. *After Eighteen Months*

Aspect	No. of Patients	Number Improved	Number Same	Number Worse	% Improved
Vascular anatomic status:					
Controls	7	2	2	3	28.5
Tiss. Extr.	7	3	1	3	42.9
Tissue anatomic status:					
Controls	6	2	3	1	33.3
Tiss. Extr.	6	2	1	3	33.3
Rest pain:					
Controls	4	0	4	0	0.0
Tiss. Extr.	7	2	3	2	28.5
Claudication:					
Controls	6	3	1	2	50.0
Tiss. Extr.	6	6	0	0	100.0
Vascular reserve:					
Controls	5	2	2	1	40.0
Tiss. Extr.	7	1	2	4	14.3
Functional class:					
Controls	6	3	3	0	50.0
Tiss. Extr.	6	4	2	0	66.7

six out of nine (66.7 per cent) improvement in claudication, eight out of 20 (40 per cent) improvement in vascular reserve, and four out of 10 (40 per cent) improvement in functional classification.

Of the control series, four out of seven (57.1 per cent) showed improvement in vascular anatomic status, one out of four (25 per cent) showed improvement in tissue anatomic status, 0 out of seven (0 per cent) showed improvement in rest pain, 0 out of six (0 per cent) showed improvement in claudication, three out of seven (42.9 per cent) showed improvement in vascular reserve, and two out of seven (28.5 per cent) improvement in functional classification.

After 12 months of treatment, of the pancreatic tissue extract treated cases, three out of 15 (20 per cent) showed improvement in vascular anatomic status, five out of 14 (35.7 per cent) showed improvement in tissue anatomic status, six out of 14 (42.9 per cent) showed improvement in rest pain, 10 out of 15 (66.7 per cent) showed improvement in claudication, three out of 15 (20 per cent) showed improvement in vascular reserve, and nine out of 15 (60 per cent) showed improvement in functional classification.

Of the control series, two out of nine (22.2 per cent) showed improvement in vascular anatomic status, 0 out of six (0 per cent) showed improvement in tissue anatomic status, 0 out of seven (0 per cent) showed improvement in rest pain, two out of eight (25 per cent) showed improvement in claudication, three out of six (50 per cent) showed improvement in vascular reserve, and two out of eight (25 per cent) showed improvement in functional classification.

After 18 months of treatment, of the pancreatic tissue extract treated cases, three out of seven (42.9 per cent) showed improvement in vascular anatomic status, two out of six (33.3 per cent) showed improvement in tissue anatomic status, two out of seven (28.5 per cent) showed improvement in rest pain, six out of six (100 per cent) showed improvement in claudication, one out of seven (14.3 per cent) showed improvement in vascular reserve, and four out of six (66.7 per cent) showed improvement in functional classification.

Of the control series, two out of seven (28.5 per cent) showed improvement in vascular anatomic status, two out of six (33.3 per cent) showed improvement in tissue anatomic status, 0 out of four (0 per cent) showed improvement in rest pain, three out of six (50 per cent) showed improvement in claudication, two out of five (40 per cent) showed improvement in vascular reserve, and three out of six (50 per cent) showed improvement in functional classification.

Summarizing these figures, one could say that the patients who were treated with pancreatic tissue extract regularly, in 3 c.c. doses twice a week for long periods of time (six to 18 months), showed improvement in claudication time and rest pain. It is interesting to note that our control cases consistently showed a greater improvement in vascular reserve than the tissue extract treated cases, as measured by thermal test or nerve block.

It should be stated here that, throughout our entire period of observation, we encountered no untoward systemic reaction in any patient following the intramuscular injection of any of the three brands of tissue extract used; a moderate number of patients complained of local pain or discomfort, of short duration, at the site of injection.

Conclusions

1. Pancreatic tissue extract, insulin-free, produced a drop in the muscle temperature of the lower extremity, with no significant effect on the skin temperature, when injected intramuscularly.

2. Pancreatic tissue extract, insulin-free, had no effect on claudication time, as measured by ergometer, within one-half hour of intramuscular injection.

3. Pancreatic tissue extract, insulin-free, injected intramuscularly in 3 c.c. doses twice a week for relatively long periods of time, from six to 18 months, produced improvement in claudication time and rest pain.

4. Pancreatic tissue extract, insulin-free, injected intramuscularly in 3 c.c. doses twice a week for relatively long periods of time, from six to 18 months, had no effect on vascular anatomic or tissue anatomic status, on vascular reserve, or on functional classification.

5. Patients receiving no specific treatment but following instructions concerning hygienic care of the feet, showed a definite degree of improvement in vascular reserve, as measured by thermal test or nerve block.

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CASE REPORTS

CALCINOSIS AND SCLERODERMA WITH PARATHYROIDECTOMY *

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Rosenberg [1] has recently reviewed the clinical features of "chalk gout." This condition, variously described as "calcinosis conscripta," "calcinosis universalis," "calcinosis syndrome," "tendinio-fasciitis calcarea rheumatica," "tendinitis calcarea," "petrificato cutis," "calcinosis interstitialis," "Raynaud's disease with calcareous degeneration," and "subcutaneous calcareous granulomata," had been previously extensively surveyed by Durham,[2] Steinitz,[3] Weissenbach, Basch and Basch,[4] Brooks,[5] Rothstein and Welt,[6] and Atkinson and Weber.[7]

In summary one may say that calcinosis is characterized by deposits of calcium in greater or lesser amounts in the skin and subcutaneous tissues. A circumscribed type is restricted to the region of the joints of the terminal phalanges and the extensor portions of the elbows and knees. A diffuse or universal type may involve extensive portions of the body surface and at times the interstitial tissue of muscle, tendon and nerve sheaths. Steinitz reports that the circumscribed syndrome is more prevalent in the elderly and more frequent in the female, the universal type in a much younger age group. Ramsdell [8] states that the latter occurs usually in the first two decades of life. In 40 per cent of the patients scleroderma and sclerodactylia are present. Vasospastic phenomena are common. The bones and joints are not as a rule involved, although deposits and contractures about the joint may limit motion.

The pathogenesis is unknown. Two theories explaining the calcium deposits are generally held. The first implies a primary alteration in calcium metabolism, and the second holds that calcium is deposited in previously degenerated connective tissue. Neither theory is conclusively demonstrated.

The treatment is unsatisfactory. Various physical and surgical procedures, dietary measures, and the administration of hormones and drugs have been equally unsuccessful. Ramsdell's [8] recent presentation of four patients with calcinosis universalis, demonstrating rapid reabsorption of the calcium deposits with improvement in the clinical picture following parathyroidectomy and hemithyroidectomy led us to the study of the calcium metabolism in our patient. The findings and the effects of parathyroidectomy are herein presented.

Case Report

L. M. was first admitted to the hospital in 1932 at the age of 24. Her family and past history were not pertinent. Her best weight, noted at the age of 20, was 130 pounds. Menstruation had begun at 12; it recurred every 28 days, lasted four days, and was regular. She had been married four years but had never been pregnant.

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Her present complaint was first noted at the age of 13, 11 years before admission. The first evidence of abnormality was the appearance of hard nodules on the left ring finger. One of these was excised at a hospital. Thereafter similar nodules appeared on both hands, feet, knees and the left elbow, varying in size from that of a small pea to that of a cherry. Some of these nodules would approach the surface and break down, discharging milky substance through the resultant sinus.

For two years prior to admission a progressive stiffness of the neck and upper extremities had been developing. At the same time, difficulty in opening the mouth was experienced. The patient thought that her skin was growing darker.

On admission, the patient appeared undernourished and weighed 96 pounds. The spine was rigid. The head was held erect but was raised with considerable difficulty. The skin of the face, neck, upper chest and arms had a glossy, indurated mottled brown appearance. It did not wrinkle. The lips were somewhat retracted.

The thyroid was palpable.

The arms were thin and displayed a loss of power with a bilateral wrist drop. Hard nodules, some of them freely movable, were noted in the hands. Similar lesions were present at the knee and in the feet. There was limited movement at the small joints, which tended to be flexed.

The systolic pressure was 104 mm. Hg; the diastolic was not obtained.

Laboratory Data. The urine, except for an occasional red blood cell and white blood cell, was negative, and the specific gravity was 1.032. The blood count was normal.

Basal metabolic rate was minus 7 per cent.

Blood chemistry was normal. The phosphorus varied from 2.1 to 3.4 mg. per cent.

Wassermann and Kahn reactions were negative.

On roentgen-ray, increased density was noted in the skull, femora and pelvis. Mottling of the upper third of both humeri was apparent. In some places there were areas of osteocondensation. Subcutaneous calcium deposits were seen in both hands, about the left elbow, both knees, particularly the left, over the head of the fourth metatarsal and over the middle of the right mandible.

A nodule together with some skin was removed from the knee. The nodule consisted of calcium 55 per cent and urates 10 per cent.

A biopsy report was as follows: "Superficial epidermal layer normal. The pigmented basal layer of the corium is very pronounced. The subcutaneous tissue is thickened by an increase of fibrous tissue. The hair follicles, sebaceous glands and sweat glands appear normal. In the deeper layer of the fibrosed tissue are spaces containing granular amorphous material. This contains occasional plaques of degenerated cells. The amorphous material takes a faint blue stain and is apparently soluble in Zenker's solution."

Following discharge from the hospital the patient attended the out-patient department for one year. Here she received some urinary gonadotropins and foreign proteins without perceptible effect. From 1933 to 1939 she attended another clinic. There minute amounts of anterior pituitary extract, thyroid extract, ammonium chloride and a ketogenic diet were haphazardly administered. No improvement was noted. Recurrent nodules formed and motion in the hands became more limited.

The patient was readmitted to the Jewish Hospital in November, 1939. The general nutrition was fair; weight was 116 pounds. The skin of the face was reddish brown in color and exhibited several irregular darker areas over the forehead and cheeks. It was glossy, indurated, and did not wrinkle. The mouth was drawn into a fixed smile, could not be completely closed, and could be opened only to a limited degree (figure 1). The skin over the neck, upper chest and arms, as well as over the knees, had the same sclerodermatous appearance. The muscles of the neck and arms were atrophied. Bilateral wrist drop was present. The head was held erect but

could be raised only with difficulty. The whole spine was stiff and evidenced limitation of motion. There was also some limitation of motion at the shoulders, elbows, hips and knees. The hands were kept flexed. Here, too, movements at the small joints were limited apparently by the collections of bony hard nodules in the subcutaneous tissue about them, and also by contractures due to tendon sheath involvement. Similar nodules varying from 1 to 3 cm. in size, conglomerate in some areas, were found on the wrists, left elbow, sole of the right foot and knees and over the dorsal spine. There were discharging sinuses over the left knee and spine. The discharge appeared purulent and somewhat chalky.

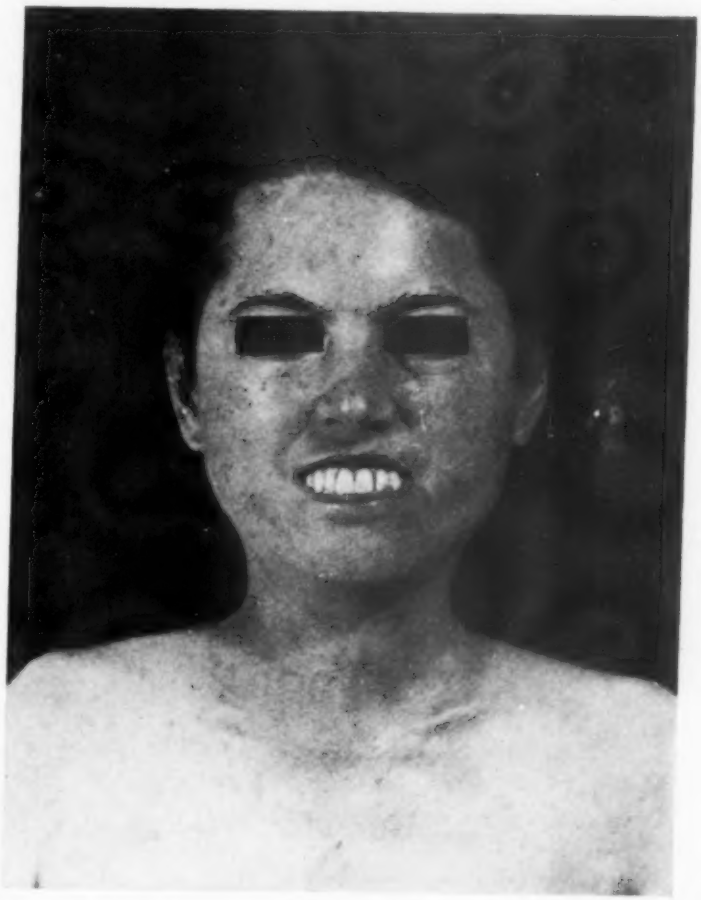

FIG. 1. Patient. Illustrating fixity of skin, atrophy and pigmentation.

The blood pressure was 140 mm. Hg systolic and 90 mm. diastolic.

The remainder of the physical examination was not pertinent. Roentgenography revealed the heart and lungs to be negative.

Rarefaction of both humeri was noted (figure 2). There was decreased thickness of the cortex and some cystic change in the upper half of the right cortex. There was thinning of the humeroscapular articulation. All the other bones appeared normal. Calcium deposits were seen in both hands (figure 3), knees, particularly the left, over

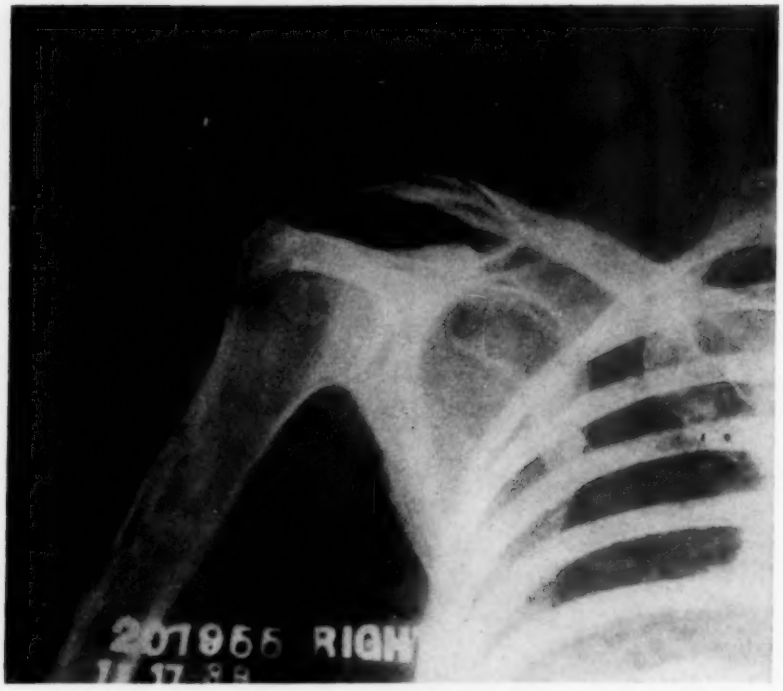

FIG. 2. Decalcification. Humerus.

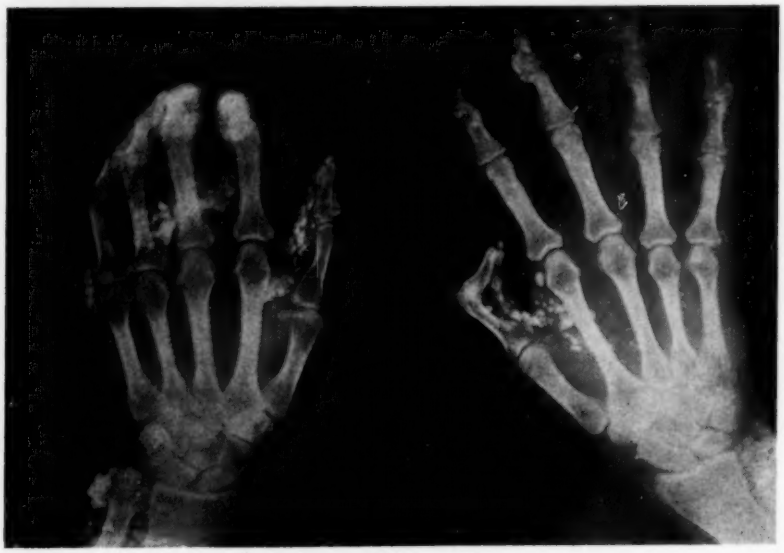

FIG. 3. Calcium deposits about phalanges and wrist.

the right third, fourth and fifth metatarsals and the left fifth metatarsal. Larger deposits were evident in the subcutaneous tissue of the left elbow (figure 4) and left knee. The bones and the joints in the region were not involved. A large deposit of calcium was seen within the abdomen opposite the fourth and fifth lumbar vertebrae.

Laboratory Data. Electrocardiograph showed some evidence of myocardial involvement. Basal metabolic rate was minus 14 per cent. Sedimentation time was 28 mm. per hour.

Urine: Specific gravity 1.020–1.030; albumin 1 plus to none; occasional white blood cell.

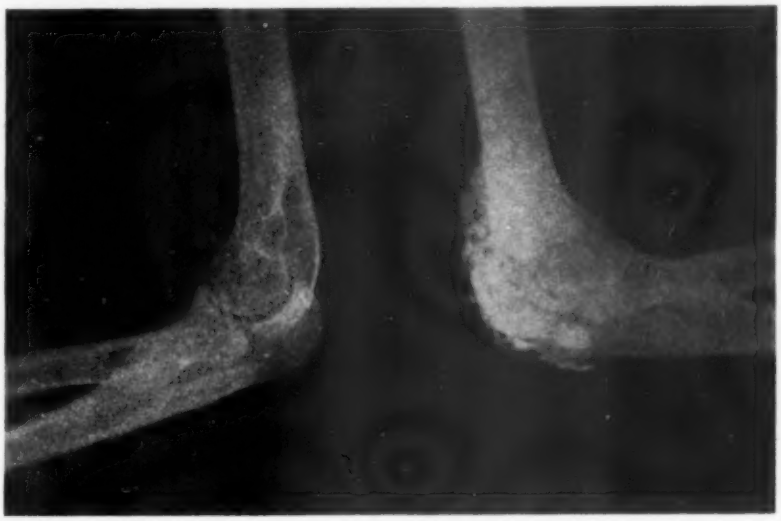

FIG. 4. Calcium deposits about elbow.

Blood: Hemoglobin 94 per cent; red blood cells 6,000,000; white blood cells 19,400; 75 per cent polymorphonuclears; no abnormal cells. Kline test was negative.

Chemistry: Sugar 78 mg. per cent; urea 9.9 mg. per cent; uric acid 4.7–5 mg. per cent; lipids 650 mg. per cent; cholesterol total: 248, free–67 mg. per cent. Urea clearance was normal. There was no arsenic in the blood. Arsenic in the urine was normal. Calcium 10.6 mg. per cent; phosphorus 3.8 mg. per cent; phosphatase 3.9 units; non-protein nitrogen 28.4 mg. per cent; total protein 7.09 gm.; albumin 4.83 gm.; A/G ratio 2.14; magnesium 2.3 mg.; total base 140 milli-equivalents.

The patient was discharged and returned the following month in January, 1940. Calcium and phosphorus balance studies on weighed analyzed diets were performed. These revealed a positive calcium balance and a tendency toward a negative phosphorus balance. The urinary and fecal excretion percentages for calcium were normal (table 1).

On January 12, 1940, under avertin and nitrous oxide-oxygen-ether anesthesia, a right hemithyroidectomy and parathyroidectomy was performed by Dr. H. Louria. Two parathyroid glands identified histologically were removed. Sclerodermatous skin and muscle biopsies were taken. The patient made an uneventful recovery. She was discharged eight days postoperatively. The calcium and phosphorus remained normal. The uric acid seven days postoperatively was 2.9 mg. per cent as compared with 5 mg. preoperatively.

TABLE I

Balance Studies

Date	Calcium Intake (in mg.)	Output (in mg.)		Total	Balance
		Urine	Feces		
1–10–40	1218	55	663	718	+500
1–11–40	996	37	500	537	+459
1–12–40	527	74	127	201	+326
Operation, 1–12–40					
1–17–40	333	44	212	256	+ 77
1–18–40	737	62			
1–19–40	698	67	(Feces Lost)		
1–20–40	875	47	269	316	+559

Date	Phosphorus Intake	Output		Total	Balance
		Urine	Feces		
1–10	494	368	296	664	−172
1–11	1020	235	624	859	+161
1–12	494	350	164	514	− 20
Operation, 1–12–40					
1–17	431	209	187	396	+ 35
1–18	768	294			
1–19	652	142	(Feces Lost)		
1–20	695	178	111	289	+406

Histology: Two normal parathyroid glands. Normal thyroid tissue.

"Specimen from the sternothyroid muscle shows pink staining tissue in which the striations of the muscle are indistinct and the muscle fibers appear somewhat swollen; the larger blood vessels show some thickening of the walls and narrowing of the lumina. No cellular infiltration.

"The sternomastoid muscle shows hyalinizing fibrous connective tissue and adipose tissue and an occasional fragment of striped muscle. The capillaries are engorged and there are foci of freshly extravasated blood. There is in places a slight scattering of small round cells and large mononuclear cells.

"Skin: In the preparation the surface is somewhat corrugated and is covered by a narrow band of stratified squamous epithelium with keratinizing superficial layers and short blunt rete pegs. Some of the cells of the basal layer contain brown pigment. In places hair follicles, sebaceous glands and sweat glands are seen in the corium. The superficial lymph spaces are narrow and about some of them there is a slight infiltration by small round cells, large mononuclear cells, an occasional plasma cell and eosinophile. Some of the smaller blood vessels are engorged. Some of the papillae are missing. With the elastic tissue stain, elastic tissue is seen to be unaffected."

Postoperative Course. During the first week after operation the patient noted increased facial mobility. The lips could be approximated about a glass, and the forehead could be slightly wrinkled. This improvement unfortunately was not progressive. Two months after operation symptoms of dullness and lack of concentration made their appearance. At the same time a profuse hair growth over the extremities occurred. The symptoms were relieved by thyroid medication. The hair growth too, became less noticeable.

Roentgenograms taken seven months postoperatively revealed no change in the calcium deposits nor in the appearance of the right humerus.

At the present time, 22 months after parathyroidectomy, there has been little change. Facial rugae are slightly more prominent. The tongue can be protruded to a greater degree. The scleroderma, nodules and contractures are unaltered. From time to time there is a discharge of milky fluid from one of the knee sinuses. The uric acid is 3.6 mg. per cent, calcium 11.4 mg. per cent, phosphorus 3.6 mg. per cent, phosphatase 2.4 units.

Comment

Investigation of this patient failed to involve the parathyroids in the pathogenesis of calcinosis. The only suggestive findings were a preoperative tendency toward a negative phosphorus balance and the findings of changes in the right humerus resembling those seen in osteitis fibrosa cystica. The calcium balance was positive. The bone changes might be explained on the basis of disuse atrophy, since there was definite limitation of motion and atrophy of the arm muscles.

The histological appearance of the skin taken from the knee in 1932, however, suggests a more probable etiology, that is, the deposit of calcium in previously degenerated tissue. However, biopsy of sclerodermatous skin from the neck taken seven years later failed to reveal any calcium. Degenerated muscle tissue likewise exhibited no calcium deposits. It seems, then, that in addition to the usual factors of favorable ionized calcium concentration, pH, CO_2, electrolyte and protein concentration and blood flow necessary for calcium deposit, the presence of some other factor, perhaps an enzyme, is required. What rôle the uric acid may play in the process gives rise to some speculation. A preoperative blood uric acid of 5 fell to 2.9 postoperatively. We have previously observed an elevated uric acid return to normal in two cases of hypercalcemia following parathyroidectomy. One of these proved to be an adenoma of the parathyroid, the other leukemia. Both were complicated by renal insufficiency.

The failure of clinical improvement and calcium reabsorption after operation further tends to eliminate the thyroid-parathyroid mechanism from the pathogenesis, still bearing in mind the possibility that thyroid administration might have interfered with such recovery. It is possible that in Ramsdell's cases the creation of a relative hypothyroidism interfered with the absorption of calcium from the gastrointestinal tract, so that the abnormal deposits were called upon to furnish calcium for the usual physiological processes. Yet the preoperative basal metabolic rate was definitely depressed in two of his patients, on the minus side in another and elevated in the fourth. In the postoperative course there was no reference to the development of hypothyroid phenomena. In our patient the hypothyroid symptoms interfered with her comfort, happiness and efficiency to such a degree that, having noted no clinical improvement after two months, we were forced to prescribe thyroid. The excess hair growth, we believe, can be ascribed to the thyroid underactivity.

Summary

A patient presenting calcinosis universalis, scleroderma and sclerodactylia, and muscle atrophy is presented.

Studies of the calcium metabolism revealed no abnormality. The phosphorus metabolism study revealed a tendency toward a negative balance.

Hemithyroidectomy and the removal of two parathyroids, histologically identified, had little influence on the clinical course and no effect on the calcium deposits.

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COR PULMONALE WITH BILATERAL ANEURYSMS OF THE PULMONARY ARTERY, INTERVENTRICULAR SEPTAL DEFECT, PATENT DUCTUS ARTERIOSUS AND TERMINAL AYERZA'S SYNDROME *

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Aneurysms of the pulmonary artery are so rare as to constitute almost a curiosity. From 1905 to the present time there have been 28,180 autopsies in Bellevue Hospital and in only one case was this lesion found. The literature has been reviewed by D'Aunoy and E. von Haam [1] and by Boyd and McGavack.[2] We have found two cases out of 111 collected with lesions similar to the one here described. One was reported by Sachs [3] and the other by Scott.[4]

Case Report

The patient (S. H.) in whom we found this lesion at necropsy was a 44-year-old Hungarian housewife. She was admitted on January 9 to the Third (New York University) Medical Division, Bellevue Hospital, because of severe hemoptysis which allegedly occurred a few hours before entrance. Her past history was uneventful. Though examined many times by physicians, she had never been told of heart disease. Four months before admission, friends called her attention to the blueness of her lips, but not until the last six weeks did she experience any symptoms. At that time she noticed dyspnea on effort, fatigue and cough. She consulted a physician who ad-

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From the Laboratories of Pathology and the Third (New York University) Medical Division, Bellevue Hospital.

ministered digitalis and told her that her blood pressure was high. Despite treatment, her symptoms increased and she sought hospitalization following the onset of hemoptysis.

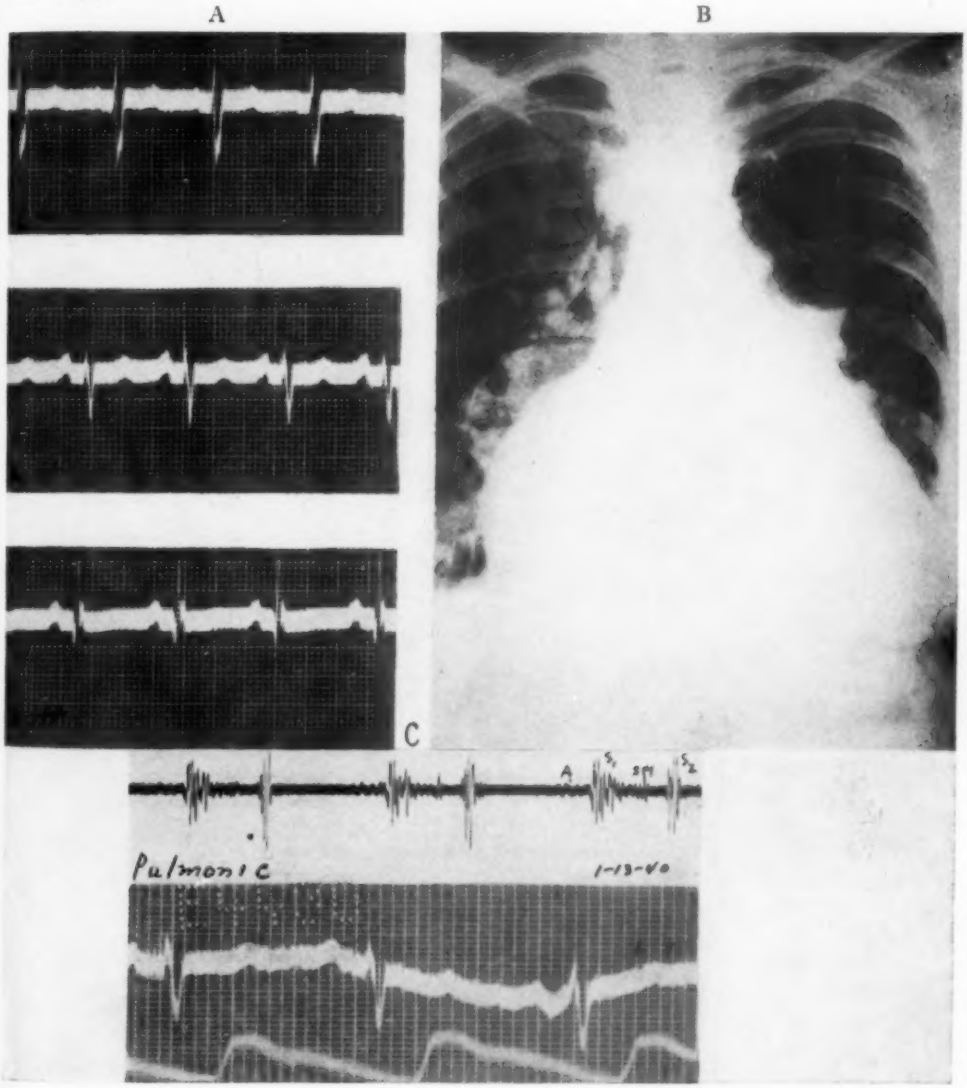

FIG. 1. A. Electrocardiogram showing normal sinus rhythm and marked right axis deviation. B. Teleroentgenogram showing the tremendous enlargement of both the right and left sides of the heart. The calcification of the pulmonary vessels is also evident. C. Stethogram showing the systolic murmur immediately following the first heart sound. The accentuated second pulmonic sound. The short diastolic murmur following this sound.

She was a small, under-developed but well nourished, white female with cyanosis of the entire body. She was dyspneic and orthopneic. She coughed frequently, raising blood streaked sputum. The jugular veins were distended and filled from below. The lungs were clear, except for a few rhonchi over the right lower lobe

posteriorly. The heart was greatly enlarged. The impulse at the apex was forceful and was seen in the fifth intercostal space in the anterior axillary line. There was a loud, harsh systolic murmur heard both at the apex and base. A short diastolic murmur was audible along the upper part of the left sternal border. The second pulmonic sound was accentuated. The rhythm was regular. The systolic blood pressure was 160 mm. Hg and the diastolic 108 mm. Hg. The liver was palpated about 5 cm. below the costal margin. The spleen was not felt. There was a moderate amount of dependent edema of the lower extremities and in the sacral region. The fingers and toes showed slight clubbing.

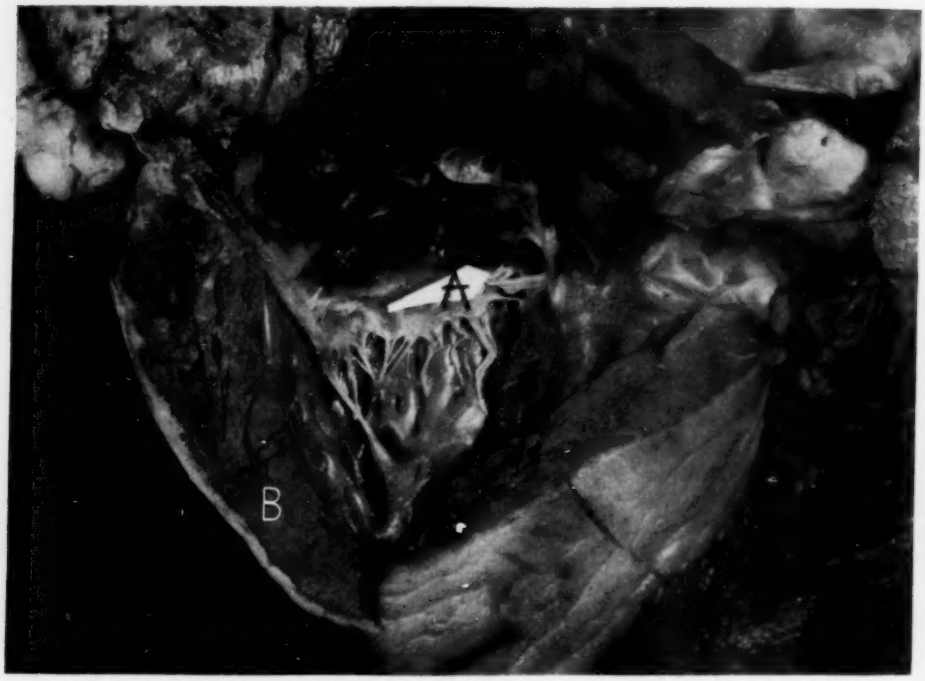

FIG. 2. View of right ventricle: A showing (patent) interventricular septal defect. Note hypertrophy of right ventricular wall at B.

The admission urine showed proteinuria. The specific gravity was 1.013 and there were many white blood cells in the sediment. The red blood cells numbered 7.14 million; hemoglobin 22 grams (154 per cent); leukocyte count and differential smear were normal. The blood Wassermann reaction was negative. Non-protein nitrogen was 53 mg. per cent, creatinine 2.6 mg. per cent. The venous pressure, taken by the direct method, was 28 cm. of water. The electrocardiogram (figure 1A) showed normal sinus rhythm and marked right axis deviation. The stethogram (figure 1C) was interpreted as recording an accentuated second pulmonic sound, a systolic murmur at the apex, aortic and pulmonic areas, and a short diastolic murmur at the pulmonic area. The teleroentgenogram (figure 1B) disclosed generalized cardiac enlargement, most marked along the right border and the outflow tract of the right ventricle. Dilatation and calcification of the right and left pulmonary arteries were evident. The left lung base was obscured by the enlarged heart shadow; at the base of the right lung were numerous small areas of increased density. The upper half of the left lung was emphysematous. Oxygen determination of arterial blood showed 30 volumes

per cent saturation; a second sample the following day after she had been kept in an oxygen tent in which the oxygen tension was maintained between 60 and 70 per cent, showed 62 volumes per cent saturation. Despite continued oxygen therapy and redigitalization there was no change in her condition. Four days after admission she became weak and comatose; the blood pressure fell to 80 mm. Hg systolic and 50 mm. diastolic; the heart sounds, however, remained loud. She died in coma on the ninth day after admission.

The significant postmortem findings were as follows: The abdomen contained 50 c.c., the left pleural cavity 300 c.c., and the pericardial sac 250 c.c. of clear yellow fluid. All the viscera showed evidence of chronic passive congestion.

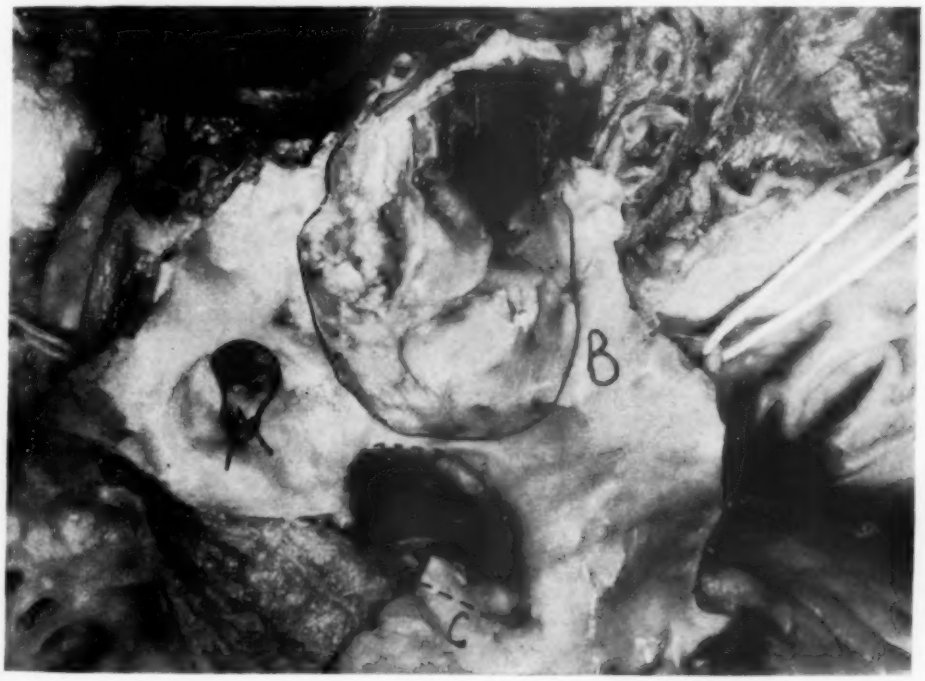

FIG. 3. A, Opening of ductus arteriosus. B, Aneurysm of left pulmonary artery. Note the organizing thrombus extending into the branch supplying the left upper lobe. C, Ostium of right pulmonary artery.

The heart was markedly enlarged both to the right and left. The apex was formed by both ventricles, the right ventricle forming about two-thirds of the anterior surface. The pericardial surface was smooth and the membrane thin. There was slight increase in the epicardial fat. The right auricle was dilated and its walls thickened. The tricuspid valves were normal in texture. Their chordae tendineae were not deformed. The right ventricle was dilated and its muscle hypertrophied, measuring at its widest portion 1.5 cm. There was a defect in the interventricular septum (figure 2) immediately below the auriculoventricular junction, measuring 0.8 cm. The foramen ovale was closed. The pulmonic ring was normal in size. The pulmonary valves were thin.

The left auricle was dilated and its wall slightly thickened. The leaflets of the mitral valve were thin and the mitral ring measured 10 cm. in circumference. The left ventricle was dilated; its musculature was 1.2 cm. thick. The aortic leaflets

showed no naked-eye changes. There were no intra-auricular or intraventricular thrombi. The coronary arteries revealed slight intimal thickening. There was no myocardial fibrosis.

The aorta was diminished in caliber and measured 3 cm. in diameter; it contained numerous small yellowish plaques. Its elasticity was well preserved. There was no evidence of syphilis. The arch communicated with the pulmonary artery through a widely patent ductus arteriosus (figure 3) which measured 1.2 cm. in diameter and 1 cm. in length. Its pulmonary ostium was located 4 cm. above the pulmonary cusps and was at the site of bifurcation of the pulmonary artery, cephalad to the right pulmonary artery.

FIG. 4. After cutting the aorta and turning the edges back, the aneurysm of the right pulmonary artery is exposed. A glass rod (C) is approximately 3 centimeters above the lower level of the aneurysm. A indicates the patent ductus arteriosus; B, aneurysm of the left pulmonary artery; and D, the interventricular septal defect.

The pulmonary conus, pulmonary artery and its branches exhibited a moderate, and in places a severe, degree of atherosclerosis with calcification. The left pulmonary artery (figure 3) was dilated prior to its entrance into the lung. This aneurysmal dilatation measured 2.5 cm. in diameter. Its wall was thin and the aneurysm was filled by a gray, laminated clot, which extended into the branch supplying the left upper lobe. This branch was also dilated, measuring 1.2 cm. in diameter. Many of its smaller rami were either completely or partially occluded by continuation of the above described thrombus. The extrapulmonary part of the right pulmonary artery (figure 4) was also dilated, forming a sac which had a depth of 3 cm. and a length of 3.2 cm. Its lumen was partially obliterated by an organized and organizing thrombus. The branch to the right lower lobe was occluded by similar blood elements. Posteriorly this aneurysm was identified by its size and upward displacement of the bifurcation of the trachea.

We believe that the two congenital arteriovenous shunts necessitated increased work on the part of the right ventricle. These shunts were also largely responsible for the pulmonary hypertension shown, clinically, by the right sided cardiac enlargement and the accentuated pulmonic second sound and, anatomically, by the right ventricular hypertrophy (cor pulmonale). This hypertension plus other unknown factors was in turn partially responsible for the degree of arteriosclerosis and calcification of the pulmonary vessels. The presence of arteriosclerosis and persistence of the ductus Botalli were undoubtedly the important factors in the development of the aneurysm of the right and left pulmonary arteries.

Furthermore, the occurrence of thrombi in the aneurysms and the gradual occlusion of many of the pulmonary vessels contributed to failure of the right side of the heart, to the increased venous pressure, and to polycythemia and progressive anoxia. It is likely that until the onset of her symptoms the patient had adequate compensation for the two arteriovenous shunts despite the partial occlusion of many of the pulmonary arteries. When the right ventricle was no longer able to maintain its output, there was reversal of flow through the ductus arteriosus and the interventricular septal defect. This accounts for the terminal cyanosis and inability to obtain a higher level of arterial oxygen saturation even under optimal external conditions.

During the last few days of her life this patient showed the syndrome described by Brenner.[5] These individuals may exhibit few or no symptoms despite the presence of widespread thrombosis of the pulmonary arteries and then expire suddenly or within a few days owing to the complete occlusion of the already narrowed vessels.

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SULFUR DIOXIDE CHEMICAL PNEUMONIA; REPORT OF A CASE WITH RECOVERY FOLLOWING ACCIDENTAL EXPLOSION OF A REFRIGERATOR UNIT*

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It is apparent that with increasing industrialization man is surrounding himself with ever increasing health hazards. Of these, one of the most important is the inhalation of irritating gas. Physicians became aware of its effect on the bronchopulmonary system during the first World War when poison gas was em-

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ployed as a weapon. Exposure has since become increasingly common in association with numerous chemical developments in industry. One of these is the use of sulfur dioxide in modern refrigeration. The toxic effects of this gas have been noted in recent reports dealing with occupational disability in the refrigerating and sulfur mining industries. These investigations were concerned mainly with the results of long continued inhalation of small amounts of the gas.[1] Chronic bronchitis and increased susceptibility to colds have been common sequelae of such exposure. Needles and Smith [2] reported on the late effects of acute sulfur dioxide poisoning in a patient who came under their observation with widespread tubular bronchiectasis and sharply reduced respiratory function. Martini, Dossola and Celener [3] have recorded the first death caused by chemical pneumonia due to sulfur dioxide poisoning. We wish to report a similar case with recovery, exemplifying (1) the rapidly destructive effect of concentrated sulfur dioxide inhalation, and (2) the apparently beneficial result of sulfonamide therapy.

Case Report

B. B., aged 15, was admitted to the Jewish Hospital November 11, 1940. The history revealed that he had found a refrigerator unit on a vacant lot and that while dismantling it, the tank blew up in his face. Further investigation showed that the fumes consisted of sulfur dioxide.

Upon admission to the accident ward about 15 minutes after the accident, the boy was very weak, dyspneic, hoarse, and unusually cyanotic. The temperature was 102.4° F., the pulse rate 140, the respiratory rate 42 per minute. There was considerable edema of the eyelids with chemosis. Widespread erosions of the conjunctivae, the nose and mouth attested to the severity of the chemical burns. The larynx was inflamed, its mucosa eroded, but there was no obstruction of the glottis. The rapid respiratory rate, the limitation of expansion in the left lower lobe, the impaired percussion note over both bases and the presence of many inspiratory râles, particularly over the left lower lobe, all indicated a rapidly progressive bronchitis and bronchiolitis. The heart was not displaced. Its action was regular but very rapid, and the sounds were of reduced volume. No murmurs were heard. The abdominal examination was negative.

Early signs of consolidation were apparent within 12 hours and frank consolidation was present in 24 hours.

Forty-eight hours after admission a roentgenogram showed a localized area of haziness obscuring the left costophrenic sulcus and extending up to the ninth rib. The roentgenologic appearance was that of a basal bronchopneumonia associated possibly with a diaphragmatic pleurisy.

The patient was placed in an oxygen tent because of his dyspnea and cyanosis. Dehydration was combated by daily venoclysis of 2000 c.c. of 5 per cent glucose in normal saline solution. The patient also received a transfusion of 250 c.c. citrated blood. He was given sulfathiazole, receiving 11 grams in 36 hours, at which time the blood concentration of the drug was 3.3 mg. per cent. The temperature began to decline from its high level of 104° and was normal on the fifth day of therapy, after 25 grams of sulfathiazole had been given. At this time the signs of pulmonary consolidation disappeared, but residual bronchitis was evident.

Roentgen-ray examination on November 25 revealed that the pneumonia had undergone complete resolution, but some intensification of the bronchial markings at the right base was evident.

Laboratory examination on November 12 showed 67 per cent hemoglobin, 3,700,000 erythrocytes, 17,600 leukocytes, of which 93 per cent were polymorphonuclears.

In the absence of productive cough, no sputum examination was made. Throat cultures revealed streptococci, staphylococci and pneumococci. The latter were type 22, a "high number type" of doubtful significance. A blood culture remained negative. There was no evidence of renal disturbance. The indirect van den Bergh was slightly elevated to 0.75 mg. per cent. (At no time was clinical jaundice noted.) We were unable to make any tests for sulfhemoglobin in the blood.

The boy was discharged on November 26, although it was thought that the cyanosis had not entirely disappeared.

Following his discharge he remained intermittently under our observation (H. G.). He suffered frequent attacks of lacrimation and sneezing. Hoarseness and cough persisted. The latter, worse in the night, was associated with morning expectoration of thick, greenish, purulent sputum. Night sweats persisted for two weeks after leaving the hospital, but there was apparently no fever except for a period of one week during the Christmas holiday. The boy complained of nervousness and extreme fatigue which prevented his return to school until early in January 1941. The school authorities thought that he had become mentally retarded.

On February 1, 1941, a roentgenogram revealed definite intensification of the lung markings in both lower lobes, especially the right. At his last follow-up examination in April 1941, the boy complained of lacrimation, although no gross conjunctival change was noted. A posterior ethmoiditis and hyperplastic pharyngitis were present. The cough and morning expectoration continued apparently unassociated with fever or weight loss. Transient râles were heard at both lung bases. In view of the continued morning expectoration of purulent sputum and the roentgenographic appearance of the lungs, bronchiectasis was considered to be present in both lower lobes. Bronchography was advised but was not done.

Discussion

Sulfur dioxide, widely used in refrigeration, is considered ideal for that purpose in that it is non-explosive and non-inflammable.[4] It is, however, one of the most irritant gases, so much so that Alice Hamilton considered it irrespirable and thus massive exposure impossible insofar as the respiratory tract is concerned.[5] This is not altogether true as evidenced by the experience of others [2, 3] as well as ourselves. In fairly high concentration the gas is corrosive, forming sulfuric acid on combining with water. Its destructive action on the moist surfaces of mucous membranes is thus explained.

Sulfur dioxide is thus similar in its action to nitrogen dioxide and tetroxide which, combining with water, give rise to another corrosive acid, namely, nitric acid.[6] Although experimental work on sulfur dioxide poisoning has not been extensive as in the case of nitrogen tetroxide and the war gases, it is believed that the pathologic changes are fundamentally alike in most of these irritant gases, possibly in all of them.[7] The great damage caused by them in both experimental animals and man is in the bronchi and bronchioles, with erosion of the lining epithelium, deciliation, edema of the underlying submucosa, spasm of the bronchial muscle and thrombosis of the small arteries and veins.[6, 8] With inhalation of concentrated fumes, the acute process extends into the alveolar ducts and the alveoli. In the latter, the inflammatory exudate consists of fibrin and plugs of desquamated cells resembling a picture of the so-called lobular catarrhal pneumonia. However, uniform lobar involvement may occur both experimentally and clinically. Death may come quickly, i.e., on the first day, as a result of pulmonary edema, somewhat later because of pneumonia. Survival over many days allows bronchial and alveolar regeneration, often attended, however,

with striking epithelial metaplasia,[6, 9] bronchial necrosis, bronchiolitis obliterans, bronchiectasis.[2] The acute erosive changes and the subsequent alterations in the course of regeneration favor bacterial invasion of the lung parenchyma. Coplin in discussing the delayed deaths in war gas poisoning said that he never saw a case in which bacteria were not abundant in the lungs, noting especially the common incidence of streptococci and gas bacilli. The latter point is important inasmuch as bacterial invasion was once not considered essential to the development of chemical pneumonia.[11]

These observations on the pathological changes are pertinent to the clinical and therapeutic considerations of such cases as our own. Our patient is one of the few instances, apparently the second recorded case, and the first to recover, of acute chemical pneumonia caused by sulfur dioxide. The symptomatology of these two cases was practically identical in its abrupt and explosive development with that noted in numerous cases of nitrogen tetroxide poisoning, and it seems reasonable to discuss them as a group in the light of recent therapeutic advances. One is impressed with the high mortality figures in reports of nitrogen tetroxide poisoning. Schubert (1911) collected 213 cases, of which 55 were fatal (24 per cent).[12] In those cases in which pneumonia was definitely present, the mortality was much higher, being 100 per cent in many small series of cases.[13, 14] The majority of these victims died within four days of exposure, often within 48 hours. The marked cyanosis and dyspnea, the rapid course, and the picture of "medical shock" are reminiscent of what was seen in the 1917–1918 pandemic of influenza. In this connection, the resemblance of the pathologic findings was commented on by Winternitz.[8, 15] The important common factors were apparently the swift local destruction of respiratory surface barriers and the subsequent collapse of resistance to mixed bacterial invasion. Physicians today possess a therapeutic weapon theoretically adequate for such a situation, namely, the sulfonamide drugs, which by their bacteriostatic action on many types of organisms allow time for the patients' recuperation and the development of humoral defense.

The administration of sulfathiazole to a patient with sulfur dioxide poisoning presented a therapeutic problem. In view of the patient's cyanosis the presence of sulfhemoglobinemia was a possibility and is considered by some to be a contraindication to sulfonamide therapy. In retrospect, we believe that sulfathiazole was highly effective. It is to be noted that in the case of Martini and Dossola, an 18 year old boy previously in good health, modern therapy consisting of oxygen, intravenous administration of glucose and saline, and a fair degree of digitalization was of no avail. A comparison based on single cases or even on small groups is inconclusive, but the data herein presented suggest that sulfonamide therapy in chemical pneumonia may be beneficial and should be administered early in effective dosage. In the absence of spectroscopic examination, the presence of sulfhemoglobin in our case remained questionable. It was noted above that early and often striking cyanosis is common to nitrogen tetroxide, chlorine and bromine pneumonitis. Occasional spectroscopic examinations, clinical and experimental, have shown that methemoglobinemia is not the cause of the cyanosis.[14, 16] The latter is due apparently to acute exudative edema interstitially and in the alveoli causing acute anoxemia.

Chronic Sequelae. With a single exception,[17] clinical reports agree on the bad chronic effect, chiefly on the bronchi, resulting from sulfur dioxide inhala-

tion. These reports are based on long range observations in the industries in which an increasing incidence of "colds," bronchitis and dyspnea has been noted despite an increasing tolerance shown by many workingmen incidental to long continued exposure.[18] In occasional constitutionally susceptible individuals bronchial asthma appears to have followed such exposure.[19, 20] Acute poisoning, if survived, should almost certainly lead to chronic bronchitis. Bronchiectasis was observed by Needles and Smith, and our patient is apparently following a similar course. Koontz,[20] basing his conclusion solely on experimental animal work, thought dogs that survived acute chemical inflammation of the respiratory tract usually made a complete recovery. It is doubtful whether such laboratory findings are entirely applicable to man. Clinical observation suggests otherwise. Bronchiectasis once established ordinarily presents a difficult therapeutic problem. It may well be that sulfonamide therapy, employed in our case with apparently striking benefit, might have been utilized in suitable dosage with equally important results in the later afebrile and subchronic stages. It is clear that bronchiectasis progresses mainly by reason of persistent infection, and prolonged small dosage of the sulfonamides may conceivably have another useful field in such cases as our own.

Summary

Concentrated sulfur dioxide inhalation may lead to acute inflammation of the respiratory tract, culminating in "chemical" pneumonia. After such exposure, a boy, aged 15, previously well, quickly showed signs of bronchopulmonary involvement. Cyanosis and dyspnea were notable features. Sulfathiazole therapy contributed to recovery, but its use limited to the acute phase of the illness did not prevent the later development of bronchiectasis.

The almost fatal accident leading to this illness was caused by the dismantling of a discarded refrigerator unit. The existence of such hazards should be publicized.

Since this article was submitted for publication, the following case has been observed.

G. T., aged 46, a junk dealer, was admitted to the Jefferson Hospital, Philadelphia, on October 6, 1941, to the surgical service of Dr. George P. Muller. The patient gave a history of hammering an old refrigerator unit which exploded with the sudden release of a gas which was considered to be sulfur dioxide. The patient was brought to the hospital within 15 minutes following the accident. At this time there were evidences of first degree burns of the face, eyes, nose and throat.

He complained of marked chest pains. He had a fever of 102° F. and a leukocyte count of 17,900 per cu. mm. A pneumonitis was suspected. Dr. Hobart Reimann found a few scattered râles in the right lower lobe. The roentgen-ray report on October 9, 1941 revealed "prominence of the hilar and parenchymal markings bilaterally, a little worse on the left side as is seen in tracheo-bronchitis."

Since his discharge on October 14, 1941 he has complained of postnasal dripping, cough and substernal pains, and the expectoration of thick mucopurulent sputum. He has become "nervous," that is, he frequently has felt "light-headed" and confused when driving his car. None of these symptoms existed prior to his accident.

He is being observed for any progressive changes in his lungs, especially early bronchiectasis.

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SUBACUTE BACTERIAL ENDARTERITIS COMPLICATING PATENT DUCTUS ARTERIOSUS: CASE REPORT WITH RECOVERY FOLLOWING SULFAPYRIDINE–HEPARIN THERAPY *

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THE following case report of recovery from subacute bacterial endarteritis is presented because it marks the successful application of the treatment of this

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usually fatal infection by combined sulfapyridine and heparin therapy. The first announcement of this ingenious combination treatment was made by Kelson and White in 1939.[1] With the publication of further controlled studies [2] a definite feeling of optimism begins to appear in the medical attitude toward the unfortunate patient afflicted with an endocardial or endarterial infection due to *Streptococcus viridans* (alpha type). In the case herein reported there was the further factor of a tuberculous infection manifested by the presence of *Mycobacterium tuberculosis* in the sputum. It is interesting to observe that the chemotherapy had no deleterious effect upon the pulmonary tuberculous infection which also apparently healed. During the period of observation after discharge from the hospital (12 months), the patient has remained in excellent health, and subsequent blood cultures have remained sterile.

Case Report

Mrs. B. D., a 45-year-old, white, American housewife, was admitted to the Tulare-Kings Counties Joint Tuberculosis Hospital on July 12, 1940 by ambulance.

The chief complaint was unexplained fever of 11 weeks' duration associated with a slightly productive chronic cough.

The patient had enjoyed fairly good health and had always worked hard until the first part of the year 1940. In January a rectal fistula had been excised by her local physician. This healed readily but left some weakness of the sphincter. She had always been bothered by episodes of rapid heart beat and "skipping of the heart" following exertion such as fast walking or the playing of games, as "far back as she could remember." Occasionally this rapid heart rate became quite irregular and persisted for as long as one to two days.

Eleven weeks prior to admission, on the night of April 22, she was awakened in the early hours of the morning by a chill followed shortly by fever and pain on both sides of the lower chest, aggravated by breathing. The "bronchial tubes felt raw and irritated" and a rather persistent cough developed, productive of slight amounts of yellow mucoid sputum. Her family physician was called and advised the patient to remain in bed, which she did for the next week. At this time she was found to have a temperature varying from 99° F. in the mornings to 101° F. in the afternoons. Intermittent chills and night sweats continued, and she became very ill. Roentgenograms revealed only "old scars" in the lung fields.

At the end of a week she had failed to improve and was sent to a consultant in a nearby city. Roentgenograms of the chest were taken and an "unresolved pneumonia" disclosed in the right lower lobe. Several roentgen treatments were given over the thorax anteriorly followed by only temporary improvement and later a return of the fever which rose to 105° F. in the afternoons and was accompanied by mental confusion.

The patient returned to her home. Occasional productive cough persisted with daily temperature elevation to 101° F. in the afternoons. She was unable to eat and became very weak. After another week at her home she was taken to a private hospital for a day where a physician took roentgenograms, following which she again returned home.

She remained in bed at home for the next several weeks with no evidence of improvement and then was removed to the local county hospital. There a blood transfusion was given following which she became stronger. After a week's observation she was referred to the Tulare-Kings Counties Joint Tuberculosis Hospital with a diagnosis of pulmonary tuberculosis.

During this illness she had lost 30 pounds in weight (170 to 140). There was occasional shortness of breath. Chills, fever and night sweats had continued. Oc-

casional respiratory pain was noted in the lower right side of the chest. Cough occurred only occasionally and was productive of a small amount of mucoid sputum. There had never been any blood-tinged sputum. There was no history of headache, joint pains or skin lesions. Occasional vomiting had occurred after forced feeding; there was no persistent nausea.

Past History. The patient was born in Missouri where she resided until the age of 36 and then came to California. Measles, chickenpox, mumps and scarlet fever (moderately severe) were reported to have occurred during childhood. She had had influenza in 1923.

At the age of 22 she was treated for "inflammatory rheumatism" over a period of six to seven months, with accompanying reddened, swollen and painful knee joints. The family physician stated that "she had had rheumatism long enough to have had a rheumatic heart." Attacks of tonsillitis were frequent during the winter months before coming to California.

Her maximum weight had been 180 pounds.

There was no history of pneumonia, pleurisy or hemoptysis. There had been no known exposure to tuberculosis. There was no history of dyspnea, orthopnea, or swelling of the feet or ankles.

Family History. The patient's father, aged 72, living and well, had arthritis. Her mother, aged 70, living and well, had diabetes mellitus and arthritis. Three siblings were living and well. There was no history of familial tuberculosis, cardiorenal disease, rheumatic fever, or thyroid disease.

Marital History. The patient's first husband was living and well. A daughter, aged 28, and a son, aged 26, were living and well. She had remarried at the age of 44. The second husband was living and well.

Social History. The patient had been occupied as housewife, mother, cafe operator and hotel housekeeper. She had done only her own housework since her remarriage two years previously.

Physical Examination (following admission). A well developed brunette woman of middle age, lying flat in bed, obviously ill and complaining frequently. The nose and mouth had a cyanotic tinge. The skin was sallow, dry, and somewhat loose. The mucous membranes were pale and slightly cyanotic. Blood crusts were present upon the septal mucous membrane. The tongue was furred. Nearly all the molar teeth were missing; the remaining ones were sound. The tonsils were adherent and cryptic, containing a few yellowish plugs. No petechiae were noted.

The thorax was thick walled and short. Examination of the heart was as follows: Point of maximum impulse was 1 cm. to left of the midclavicular line in the fifth interspace; it was rather forceful in character. Left border of dullness was 9 cm. from the midsternal line. The right border of dullness was only slightly outside the sternal margin. A systolic murmur was present along the left sternal border. A continuous type murmur was present in the pulmonic area, of loud whirring "machinery" type during systole. Pulmonic second sound was accentuated and louder than the aortic second sound. The heart sounds were of fairly good quality. No thrills were detected. The rhythm was regular, rate 90 per minute. The pulses were equal, of good volume, regular rate and rhythm. The vessel walls were soft. Blood pressure was 125 mm. Hg systolic and 75 mm. diastolic.

Lungs: There was limited expansion of the entire right side of the chest. Tactile fremitus was slightly decreased over both bases. Resonance was diminished over these same areas. The breath sounds on the right side were of decreased intensity and of bronchovesicular character. Scattered crepitant râles were heard beneath the right scapula and in the right axilla. A few coarse râles were heard at the left base posteriorly and anteriorly. Whispered voice was slightly increased over the right base, unchanged on the left. Diaphragmatic excursion was limited on the right side.

The abdomen was rotund, with soft, obese walls. There were a few striae albicantes. The lower edge of the liver was just palpable beneath the right costal margin. The spleen was slightly enlarged. There were no areas of tenderness.

The extremities showed evidence of weight loss. The nail beds were faintly cyanotic. There was no curvature or clubbing of the fingernails. An old, healed scar tract extended into the anal opening. Digital examination was negative.

The temperature was 101.2° F., respiratory rate 20, pulse rate 90. An occasional cough occurred, with little or no production of sputum.

During the few days following admission the patient felt better but continued to have frequent, mild chills and a temperature varying from 98° F. to 101° F. and 103° F. daily. A roentgenogram of the chest made on July 13, 1940, the day after admission (figure 1), revealed irregular patches of consolidation in the lower two-thirds

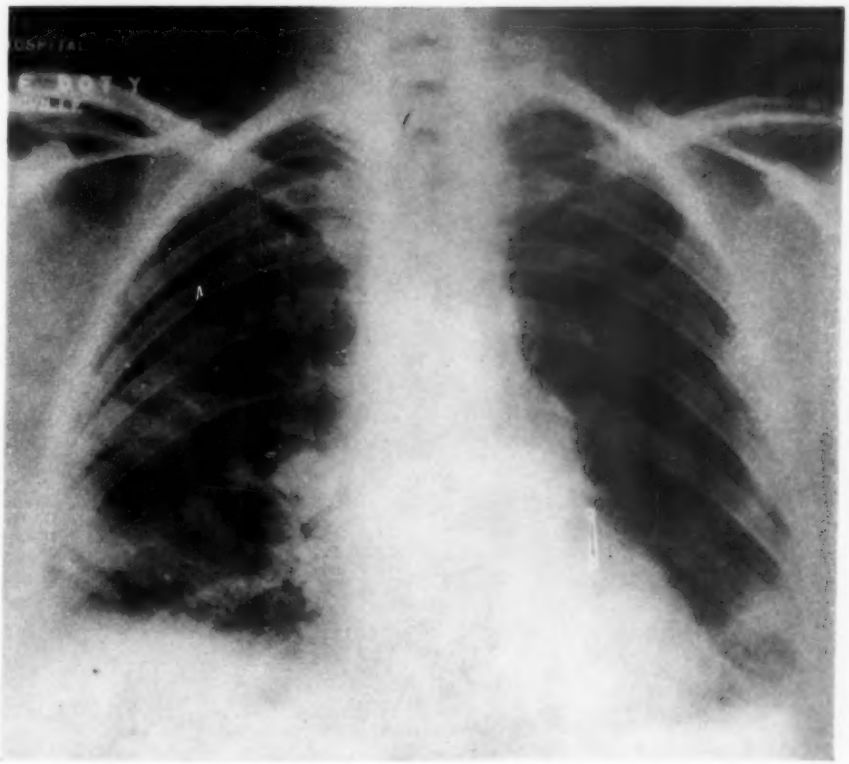

FIG. 1. Roentgenogram of chest taken on admission, July 13, 1940.

of the right lung field and in the left base. Old fibrosis was also present in the lower third on the right. There were calcified pulmonary foci outside the left hilus. The heart lay transversely, and there was prominence of the pulmonary conus. The aortic knob protruded and showed evidence of calcification. The impression was pneumonitis of unknown etiology, chronic passive congestion and cardiac dilatation and hypertrophy.

A specimen of sputum obtained three days after admission was concentrated and tubercle bacilli demonstrated by the Ziehl-Neelson stain (Gaffky II). The Gram stain revealed large numbers of gram-positive cocci in chains. The Kline reaction was negative.

Examination of the urine showed a light cloud of albumin, and microscopically there were 40 to 50 red blood cells and 8 to 10 white blood cells per high power field. A few coarse granular casts were also noted.

The red blood cell count was 5,100,000, and there were 12 gm. of hemoglobin (71 per cent Sahli) per 100 c.c. The white blood cell count was 13,450 with mature neutrophiles 76 per cent, immature 6 per cent, lymphocytes 13 per cent and monocytes 5 per cent. The red blood cells were essentially normal in size and appearance. A blood sedimentation rate (Brooks) was pathologic with 37 per cent settling at the end of 60 minutes.

On July 17, 1940, five days after admission, a blood culture was made which after five days' incubation revealed a pure growth of *Streptococcus viridans* (alpha). This was confirmed a few days later by a second culture taken on July 22, 1940, which contained 13 colonies of *Streptococcus viridans* per c.c. on the blood agar plate.

Following the demonstration of tubercle bacilli in the sputum and *Streptococcus viridans* in both blood cultures, a diagnosis of active pulmonary tuberculous infection was considered, plus patent ductus arteriosus complicated by subacute bacterial endarteritis (*Streptococcus viridans* (alpha)). The pulmonary pathology was considered the result of septic embolic phenomena arising from the vegetative endarteritis of the ductus arteriosus. In this respect the roentgenogram was quite typical of bilateral basal pulmonary infarcts. The extent of the pulmonary tuberculous infection was considered to be very minimal and difficult to delineate by the roentgenographic appearance.

Reference to figure 2 will disclose the further important laboratory studies during the course of treatment. It graphically illustrates the temperature reaction to the blood stream infection and the response to different sulfonamide therapies.

On July 23, 1940, the twelfth day of hospitalization, sulfanilamide was started as indicated in figure 2. This was followed in 24 hours by nausea, vomiting, increasing cyanosis, vertigo and mental confusion. The blood pressure fell to 100 mm. Hg systolic and 60 mm. diastolic, and there was little response to the therapy although a blood concentration of only 6 mg. per cent was reached. Therefore, it was discontinued on the fourth day.

A week later the patient appeared slightly improved and less toxic. The cardiac murmurs persisted unchanged; the blood pressure rose to 110 mm. Hg systolic and 60 mm. diastolic. She had a return of the sharp pleuritic pain at the left pulmonary base, relieved by strapping the chest. Because of the increasing secondary anemia, she was transfused with 500 c.c. of citrated blood on the twenty-third day of hospitalization, and placed on iron and vitamin B therapy.

During the following three weeks she gradually failed, becoming more toxic and showing persistent cyanosis. There was occasional cough productive of a slight amount of mucoid sputum. She continued to complain of frequent chest pain in the left base and once in the right apex.

A second chest roentgenogram, taken on August 24, 1940, showed evidence of clearing and decrease in the size of the areas of consolidation on the right side. The heart remained generally enlarged and the vascular markings accentuated in both hili.

On the forty-ninth day there was a marked secondary anemia. The urinary findings were continuously abnormal with persistent microscopic hematuria and albuminuria. A third blood culture, made on August 29, 1940, disclosed 10 to 12 colonies of *Streptococcus viridans* per c.c. During the afternoon of this day the patient complained of sudden severe precordial pain accompanied by mild orthopnea and decrease in pulse volume. There was moderate cyanosis of the face and she appeared apprehensive. The pain gradually became less severe but persisted for 36 hours. No pericardial rub could be heard, but a coronary embolic phenomenon was considered possible. A second transfusion was given.

On the following day sulfathiazole was begun followed by a drop in temperature and the onset of nausea and vomiting. After 36 hours, conjunctivitis appeared, associated with small conjunctival hemorrhages and edema of the eyelids. A rash, beginning on the index fingers, spread to the arms, thighs, legs, and forehead and became so marked and painful that the drug was discontinued after three days of use. A fourth blood culture taken at this time was positive for *Streptococcus viridans*, there being one colony per c.c. (sulfonamide present in blood). Red cells, white cells, albumin and casts persisted in the urine.

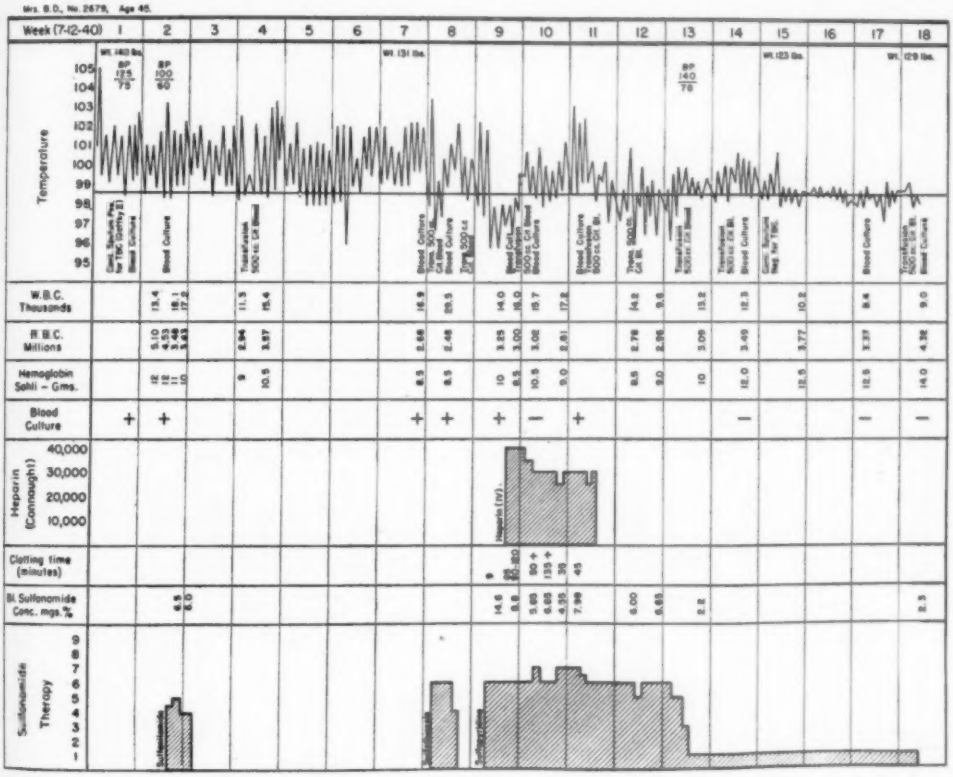

FIG. 2.

Correspondence with Dr. Paul D. White of the Massachusetts General Hospital, concerning the clinical history and course of this patient's illness, encouraged us to proceed with further active treatment. Influenced by the paper of Kelson and White,[1] we had sought this direct consultation and through the courtesy of Dr. White were advised to combine sulfapyridine and heparin, using the method described in the paper by Kelson and White.

All medication except vitamins was stopped and sulfapyridine started at noon on September 7, 1940, on the fifty-seventh day of hospitalization. The dosage was regulated by blood concentration determinations. This was followed immediately by a drop to subnormal temperatures. The administration of intravenous heparin (Connaught) solution was started on the fourth day following the beginning of sulfapyridine, when a blood level concentration of 14.6 gm. per cent had been reached. A fifth blood culture taken on September 10, 1940, showed one colony of *Streptococcus viridans* per 3 c.c. of blood (despite sulfonamide present in blood).

The blood clotting time previous to heparinization by the "5 tube method" was recorded as nine minutes.

Heparin was added to either 10 per cent or 2½ per cent dextrose in normal saline, starting with 20,000 units (20 c.c.) to each liter flask of dextrose solution, and using two flasks (liters) per 24 hours, thereby administering 40,000 units of heparin for the first few 24 hour periods. This resulted in a rapid increase in the clotting time, which at first became excessive (90 to 120 minutes) and from then on the amount of heparin given was reduced and varied according to the clotting time (see figure 2). A clotting time of at least 45 minutes seemed desirable. Ascorbic acid was also given in daily doses of 150 mg. by mouth.

The intravenous administration of heparin was continued for a period of two weeks without interruption. Sulfapyridine was continued in doses of 5 to 7 grams per 24 hours, for 26 days, and then decreased to a maintenance dose of one gram per 24 hours. This small dose was continued for two months after the patient left the hospital for a total administration time of slightly over three months. It was then voluntarily discontinued because the patient stated that it made her "short of breath."

Blood cultures were repeated at intervals, as shown in figure 2, and three negative cultures obtained before discharge from the hospital.

There was marked clinical improvement in the appearance of the patient on the third day following the beginning of heparinization. She talked and joked freely and developed a good appetite. Supportive transfusions were given (see figure 2). The basal systolic murmur became less intense; the spleen remained palpable. There was occasional chest pain beneath the right axilla. On September 24, 1940, the intravenous administration of heparin was stopped. At least 30,000 units per 24 hours had been necessary to keep the clotting time between 30 and 45 minutes. Shortly thereafter, a period of afternoon temperature elevation followed (see figure 2), accompanied by pain over the spleen (? infarct) and occasional nausea and vomiting. Some tenderness to palpation was present in the splenic area but this subsided in the next four to five days.

The patient continued to improve until September 29, 1940, the sixth day following cessation of heparin when, after eating luncheon, she suddenly broke out in cold perspiration and complained of marked cardiac palpitation, dyspnea, and precordial pain. The pulse rate at the apex and wrist was so rapid it could not be counted. She was given 1/120 gr. of strophanthin intravenously and 1/32 of dilaudid subcutaneously. The pulse rate decreased to 160 beats per minute and four hours later she vomited and the cardiac irregularity ceased. Auricular premature beats were present for the next 24 hours and then disappeared.

Two weeks later the patient was well enough to have chair and blanket privileges. The blood pressure was 140 mm. Hg systolic and 78 mm. diastolic. The cardiac sounds were of fair quality and regular in rhythm. The systolic murmur was less intense over the mitral area and was still directed toward the base where it became a loud continuous cardiac murmur. No thrills were present. The diastolic murmur remained faint and was best heard following slight exercise. There was no cough, expectoration or chest pain.

Three weeks later the spleen was no longer palpable, and temperature, pulse, and respiration were essentially normal. She had gained six pounds in weight and looked like a new person. Blood cultures remained negative. The patient was again transfused and discharged home by automobile on November 21, 1940, after 124 days of hospitalization.

Following discharge she has returned periodically to the Out-Patient Department for follow-up observation. Sulfapyridine (1 gm. per day) was stopped by the patient on January 13, 1941. A repeat blood culture on January 23, 1941 was negative for

bacterial growth. Blood studies on that day were as follows: Red blood cell count 5,350,000, hemoglobin 74 per cent (Sahli), white blood cell count 9,250. She had felt occasional slight irregularity of the heart beat. There had been no dyspnea on exertion, no edema, cough or chest pain. The blood pressure was 136 mm. Hg systolic and 82 mm. diastolic. A blood culture was repeated on April 2, 1941 and was again negative for growth. The cardiac murmurs remained unchanged. The last roentgenogram taken on June 27, 1941 (figure 3) revealed clearing in both bases with a few

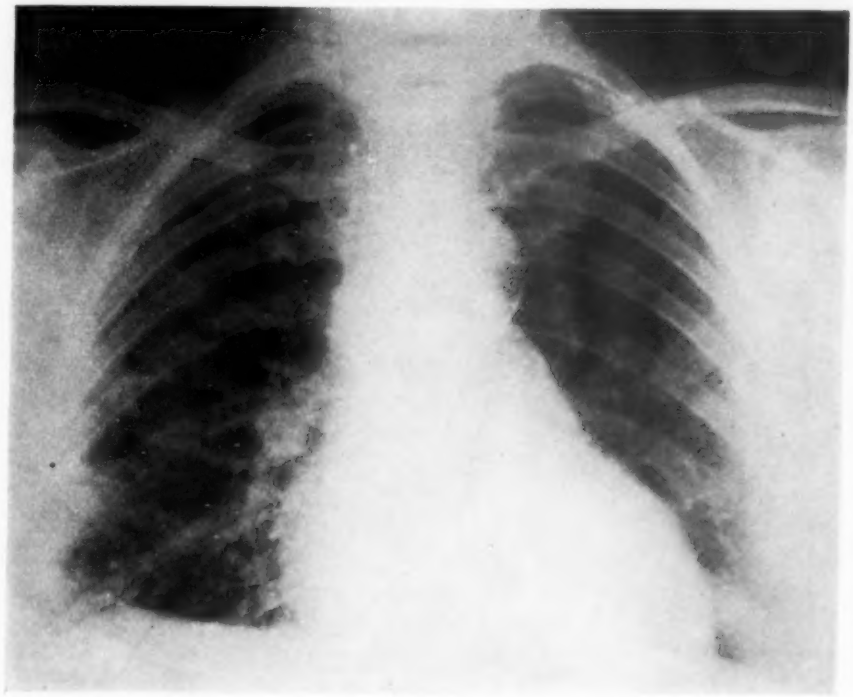

FIG. 3.

persistent strands of organization on the right. There was little change in the size or shape of the heart which still appeared somewhat generally enlarged. The patient was in excellent health and spirits and was leading a quite normal and only slightly restricted life.

She was last examined on October 25, 1941 and had gained in weight to 188 pounds and appeared in good health. There had been occasional short periods of cardiac irregularity. No cough, chest pain, or edema was noted. There was no dyspnea on exertion. A roentgenogram revealed no important change in the appearance or size of the heart or within the lung fields since the previous film. An electrocardiogram was normal with no evidence of axis preponderance.

On October 30, 1941, the patient was seen by Dr. Paul D. White at Stanford University Hospital. He found no evidence of rheumatic valvular disease but made a diagnosis of patent ductus arteriosus.*

* The patient was last seen on September 23, 1942 and was in excellent health. The cardiac murmur persisted unchanged and a roentgenogram of the chest revealed well healed fibrosis in both bases of the lungs. The cardiac outline revealed slightly more prominence of the pulmonary conus.

Discussion

In this case there were two infections, namely, the tuberculous one and bacterial endarteritis of alpha-hemolytic streptococcus type complicating a congenital cardiac defect (patent ductus arteriosus). Of the two separate disease processes the blood stream infection was the more important from the standpoint of preservation of life. This called for energetic treatment if a fatal outcome were to be averted. The pulmonary tuberculous infection was of secondary consequence.

In view of the successful outcome and apparent cure of the bacterial endarteritis in this case, further support is added to the idea advanced by Kelson and White in combining sulfapyridine and the anticoagulant effect of heparin in the treatment of this highly fatal disease. The pulmonary tuberculous infection was not unfavorably influenced by this therapy; to the contrary, it became quiescent as manifested by roentgenographic improvement and conversion of positive sputum.

The pulmonary pathologic changes must be considered as considerably complicated. The following elements enter the picture: namely, the passive vascular congestion of the lungs secondary to possible myocardial failure, the occurrence of septic pulmonary emboli, and the existence of a tuberculous infection manifested by acid-fast bacilli in concentrated sputum. It would be difficult to delineate one from the other by the pulmonary roentgenogram. It is conceivable that the tuberculous infection was a minor one, perhaps a "lighting up" of an old imperfectly healed pulmonary focus occurring as a result of the acute congestive and embolic pulmonary processes.

Summary

Subacute bacterial endarteritis engrafted upon a patent ductus arteriosus and associated with a mild pulmonary tuberculous infection is reported in a woman of 45.

Treatment by sulfapyridine and the anticoagulant heparin in combination, according to the method of Kelson and White, resulted in sterilization of the blood stream and complete recovery from both the endarteritis and the tuberculous infection. Follow-up studies over a period of one year following discharge from the hospital are fully confirmative of the effectiveness of the therapy.

The authors wish to note their appreciation and indebtedness to Dr. Paul D. White for helpful criticism and advice, both in the treatment of the patient and in preparation of the paper.

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EDITORIAL

POSSIBLE SUBSTITUTES FOR HUMAN PLASMA

THE need for huge quantities of human plasma in the treatment of war injuries has naturally stimulated the search for material from some foreign species of animal which would serve as a suitable substitute. It has been shown in human as well as animal experiments that serum or plasma of the horse or cow is effective in the treatment of shock in individuals who tolerate it. The risk of immediate serious reactions, however, as well as its property of sensitizing individuals to future injections, preclude the use of unaltered foreign serum or plasma.

Wangensteen and associates [1] have reported a study of the effect of injections of bovine serum or plasma in 120 human subjects, chiefly cases of inoperable carcinoma. Individuals giving a positive intracutaneous reaction to bovine serum were excluded for the most part, as they "did not take serum well." Three patients with negative intracutaneous tests, furthermore, suffered violent anaphylactic reactions, and over 60 per cent of the subjects had immediate reactions less severe in type. Two patients who were in shock, however, showed a rise in blood pressure after the injections, and metabolic studies in some cases were reported as indicating that some protein was retained and utilized.

Horse serum is less toxic than bovine serum, in animal experiments about one-fifth as toxic, but is still unsafe for therapeutic use.

Many efforts have been made to eliminate these reactions. For the most part these have sought either to separate the various proteins in plasma, usually by fractional precipitation, and discard the fractions which are most toxic and antigenic; or so to alter the protein molecule by physical or chemical means as to eliminate its specificity and antigenicity without actually destroying the molecule.

It has long been known that plasma albumin and plasma globulin are antigenically distinct, and that the globulin is much more highly antigenic than the albumin. That is, the minimal dose of serum albumin which will sensitize an animal, and also the minimal dose which will cause fatal shock in a sensitized animal, are much greater than the corresponding doses of globulin. Studies in animals indicate that the difference may be about 100 fold. Essentially the same ratio probably applies to man.

Janeway and Beeson,[2] who studied the effect of a purified bovine plasma albumin solution in dogs, mention its administration to 16 human cases without reactions. Davis, Eaton and Williamson [3] also report administering

[1] KREMEN, A. J., HALL, H., KOSCHNITZKE, H. K., STEVENS, B., and WANGENSTEEN, O. H.: Studies on the intravenous administration of whole bovine plasma and serum to man, Surgery, 1942, xi, 333–355.

[2] JANEWAY, C. A., and BEESON, P. B.: The use of purified bovine albumin solutions as plasma substitutes, Jr. Clin. Invest., 1941, xx, 435 (abstract).

[3] DAVIS, H. A., EATON, A. G., and WILLIAMSON, J.: Transfusion of bovine serum albumin into human beings, Proc. Soc. Exper. Biol. and Med., 1942, xlix, 96.

beef albumin solution to 13 human cases without reaction. Keys, Taylor and Savage [4] state, however, that they have found no natural foreign protein fraction which does not cause reactions in some individuals. The albumin fraction caused the least reaction, although it sensitized readily to subsequent injections. A person sensitive to one species of foreign protein was often sensitive to other species but not necessarily to all. They found intracutaneous tests useful in selecting a suitable species of foreign protein solution for use in a given patient. Albumin solution restored animals shocked by bleeding, it remained in the circulation for days, and behaved physically like the individual's own protein.

Such observations indicate that the use of purified albumin solutions eliminates a large proportion of the reactions caused by whole serum or plasma, but not all of them, and that albumin sensitizes to subsequent injections of itself. Practically its use at present appears limited to emergencies when homologous plasma is not available, and to individuals giving a negative intracutaneous reaction.

Quantitative studies in animal experiments support this conclusion that natural albumin solutions are too highly antigenic for safe general use. The early studies of Doerr and Russ and of Wells on guinea pigs, as well as those of later observers, showed that the minimal sensitizing dose of horse serum is about 0.00001 c.c., and the minimal (intravenous) shocking dose, 0.01 c.c., although smaller amounts cause milder reactions. Normal human beings are much less sensitive than guinea pigs, but those persons who are spontaneously allergic may be extremely hypersensitive. Death has been reported after the intradermal injection of one-twentieth of a c.c. of horse serum. To be reasonably safe for sensitive persons, it would seem necessary that the antigenic activity of the material in a liter of protein solution should not exceed that of 0.01 c.c. or at most 0.1 c.c. of normal horse serum. This would be a reduction of 100,000 fold. Since the substitution of albumin for whole serum accomplishes only about a 100 fold reduction, some means of altering the protein must be sought. A suitable procedure must accomplish two objectives. It must reduce the capacity of the material to cause shock in animals sensitive to whole serum, a deviation of specificity, or "despeciation"; and it must reduce the ability of the treated protein to sensitize normal animals against itself, a destruction of all its antigenic properties.

Some degree of loss of antigenicity has been obtained by the use of heat, and in greater degree by acidification or alkalinization, and by controlled peptic digestion. Coghill and associates [5] used taka diastase in order to reduce the shocking power of the horse serum in diphtheria antitoxin. At the expense of about half of its antitoxin content, they obtained a product

[4] KEYS, A., TAYLOR, H. L., and SAVAGE, G.: Utility of animal blood in preparation of plasma for transfusion, Jr. Am. Med. Assoc., 1941, cxvii, 62.

[5] COGHILL, R. D., FELL, N., CREIGHTON, M., and BROWN, G.: The elimination of horse-serum specificity from antitoxins, Jr. Immunol., 1940, xxxix, 207–222.

whose power to shock guinea pigs sensitized to normal horse serum was reduced to about one three-hundred-and-twentieth of the original. He was unable to cause fatal shock with any dose which was not fatal to the control animals, and stated that these results were being largely confirmed by studies in man.

Smetana and Shemin [6] showed that photo-oxidation in the presence of hematoporphyrin destroyed the antibodies in certain immune sera and destroyed the antigenic properties of egg albumin. Special studies indicated that the protein molecules were altered rather than disintegrated.

Henry [7] has recently reported using this procedure in an attempt to alter the antigenicity of normal horse serum. The best results were obtained by exposing thin layers of serum to ultraviolet light in the presence of hematoporphyrin for a 96 hour period. He then studied quantitatively the capacity of the oxidized serum to stimulate precipitin formation in rabbits, to sensitize guinea pigs, and to intoxicate guinea pigs sensitized to horse serum. It was easier to secure a deviation in specificity than a loss of all antigenic activity. However, the active antigenicity of the treated serum was only about one ten-thousandth of the original. The residual material which retained the antigenicity of the original horse serum was the equivalent of 0.01 c.c. per liter. These figures closely approximate those which theoretically are the maximum consistent with reasonable safety for use in man. Thus far, however, no reports have appeared as to the actual toxicity or therapeutic efficacy of the treated serum in human experiments. Possibly the application of this procedure to the albumin fraction of horse serum might yield a safer product than that obtained from whole serum.

Chemical study of the oxidized serum showed that tryptophane had been removed from the molecule. The greater part of the original protein, however, was still precipitable by the usual reagents. Studies by means of electrophoresis and ultracentrifugalization indicated a polydispersion of the protein; that is, a marked variation in the size of the different protein molecules with the presence of large aggregates two to three times the size of the original molecules. It seems probable, therefore, that there had been an alteration rather than an actual break down of the molecules. If tests in man show that the antigenicity has been sufficiently reduced, it may be hoped that the protein in the treated serum will remain in the circulation and adequately replace homologous plasma in the emergency treatment of shock.

There are as yet no adequate observations to show to what extent such foreign protein can participate in satisfying the nutritional needs of the body. The importance of this function of the plasma proteins has been emphasized by Whipple and has been previously discussed here.[8] Earlier

[6] SMETANA, H., and SHEMIN, D.: Studies on photo-oxidation of antigen and antibodies, Jr. Exper. Med., 1941, lxxiii, 223–242.

[7] HENRY, J. P.: Quantitative studies of the photochemical despeciation of horse serum, Jr. Exper. Med., 1942, lxxvi, 451–476.

[8] Editorial: Plasma proteins, ANN. INT. MED., 1940, xiv, 533.

work of Holman, Mahoney and Whipple [9] indicated that in dogs homologous plasma protein was retained and utilized but foreign plasma (unaltered) was not. Recent observations of Elman and Davey [10] in dogs cast doubt on their ability freely to utilize even homologous plasma protein administered intravenously. If the altered foreign protein cannot be utilized effectively in nutrition, its value would be distinctly limited. The experiments already reported, however, warrant the hope that a procedure will be perfected which will render foreign serum safe from the standpoint of immediate reactions and suitable at least for use in emergencies.

[9] HOLMAN, R. L., MAHONEY, E. B., and WHIPPLE, G. H.: Blood plasma protein given by vein utilized in body metabolism; dynamic equilibrium between plasma and tissue proteins, Jr. Exper. Med., 1934, lix, 269–282.

[10] ELMAN, R., and DAVEY, H. W.: Studies on hypoalbuminemia produced by protein-deficient diets. III. The correction of hypoalbuminemia in dogs by means of large plasma transfusions, Jr. Exper. Med., 1943, lxxvii, 1–5.

REVIEWS

Formulary and Handbook of The Johns Hopkins Hospital. Edited by JOHN C. KRANTZ, JR. 253 pages; 11.5 × 17.5 cm. John D. Lucas Co., Baltimore. 1942. Price, $2.00.

The material in this book was originally compiled by members of the staff representing the various departments of the Johns Hopkins Hospital, primarily for the guidance of interns and residents in prescribing drugs and other therapeutic measures. In effect it is an abbreviated pharmacopeia and formulary, including only those drugs and mixtures which are regarded as important and which are actually in general use in the wards and dispensary in each of the principal departments of the Hospital. The number of preparations considered is therefore limited to a relatively small group which have survived a long period of natural selection.

Each preparation is described, indications for its use are stated, as well as dose and directions for administration. In separate sections are included special drugs and mixtures used in the departments of urology, gynecology, dermatology, ophthalmology, and laryngology. Vitamins, endocrine preparations and biological products are included, as well as diagnostic agents. Directions are given for a few special therapeutic procedures such as transfusion. There is also a short section giving treatment of the commoner types of poisoning.

The book contains a surprising amount of useful information, easily available, and "ballast" has been almost entirely eliminated. It is not designed as a textbook, but will be very useful for the purpose for which it was intended.

P. W. C.

Fever Therapy Technique. By JACK R. EWALT, M.D., ERNEST H. PARSONS, M.D., STAFFORD L. WARREN, M.D., and STAFFORD L. OSBORNE, M.D. 161 pages: 13 × 19 cm. Paul B. Hoeber, Inc., New York. 1939. Price, $2.50.

This book of 154 pages of text contains a concise, lucid exposition of the various methods of inducing fever for therapeutic purposes. In only one respect do I take exception to the views of the authors. This is in their criticism of those who object to the "one day fever plus chemotherapy" scheme of treatment of syphilis. The authors may recall that this form of therapy has been used in Europe with poor results, in that numerous relapses have occurred. Although it is desirable that methods designed to hasten a cure should be investigated, the results thus far obtained do not warrant criticism if we advise patients against too great an enthusiasm for this form of treatment at the present time.

On the whole this book is a desirable compend for the physician who expects to use fever therapy.

H. M. R.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Hospital Care of the Surgical Patient. By GEORGE CRILE, JR., M.D., and FRANKLIN L. SHIVELY, JR., M.D. With a Foreword by Evarts A. Graham, M.D. 184 pages; 22 × 14.5 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, $2.50.

What the Citizen Should Know about Wartime Medicine. By JOSEPH R. DARNALL, M.D., Lieutenant Colonel, Medical Corps, United States Army and V. I. COOPER.

237 pages; 21 × 14 cm. 1942. W. W. Norton & Company, Inc., New York. Price, $2.50.

Mind: Perception and Thought in Their Constructive Aspects. By PAUL SCHILDER. 432 pages; 22 × 14.5 cm. 1942. Columbia University Press, New York. Price, $5.00.

Goals and Desires of Man. By PAUL SCHILDER. 305 pages; 22 × 14.5 cm. 1942. Columbia University Press, New York. Price, $4.00.

Mental Health in College. By CLEMENTS C. FRY, M.D., WITH THE COLLABORATION OF EDNA G. ROSTOW. 363 pages; 23.5 × 16 cm. 1942. The Commonwealth Fund, New York. Price, $2.00.

The Hemorrhagic Diseases and the Physiology of Hemostasis. By ARMAND J. QUICK, PH.D., M.D. 340 pages; 25 × 16 cm. 1942. Charles C. Thomas, Springfield, Illinois. Price, $5.00.

Infant and Child in the Culture of Today. By ARNOLD GESELL, M.D., and FRANCES L. ILG, M.D., IN COLLABORATION WITH JANET LEARNED, M.A., and LOUISE B. AMES, PH.D. 399 pages; 26 × 19.5 cm. 1943. Harper & Brothers, New York. Price, $4.00.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,122 Fellows and Associates of the College on active military duty. Herewith are reported the names of 96 additional members, bringing the grand total to 1,218.

Ladislaus L. Adamkiewicz
Frank W. Anzinger
Karl F. Arndt

Justus M. Barnes
Lawrence H. Beizer
Joseph E. Brackley
Henry A. Bradford
Edward S. Brewster
Hildahl I. Burtness
Otto L. Burton

John R. Cavanagh
Augustus H. Clagett, Jr.
H. Dick Countryman
J. Antrim Crellin
George R. Crisler

Constance A. D'Alonzo
Joseph H. Delaney
Albert H. Douglas
Joseph L. Duffy
J. Richard Durham

Joseph C. Ehrlich
Ephraim P. Engleman
William D. Evans

I. Donald Fagin
Isidore A. Feder
Lester C. Feener
Frederick W. Fitz
Frank P. Foster

John L. Gompertz
Edgar S. Gordon
Clark C. Goss

Frederic W. Hall
Mason V. Hargett
Robert M. Harris
Harold E. Hathhorn
Carl C. Hoffman, II
Ellis H. Hudson
Samuel Hurwitz

Thomas C. Jaleski
Frederick A. Johansen
Frank T. Joyce

Clyde H. Kelchner
Ernest Q. King
Roy E. Kinsey
Carl J. Kornreich
Alfred L. Kruger

Byrd S. Leavell
Harris V. Lilga
Louis S. Lipschutz
Joseph H. Low
Clayton J. Lundy
Charles H. Lutterloh

Frank R. Maddison
Robert C. Manchester
Edward A. Marshall
Walter P. Martin
Thomas C. McCleave, Jr.
James W. McElroy
Frank B. McGlone
Samuel Melamed
William C. Menninger
William C. Meredith
Saul Michalover
Laurence C. Milstead
Norman L. Murray

Robert A. Newburger

J. Frederick Painton
Harry Parks
J. Winthrop Pennock
Thornton T. Perry, III

George N. Raines
Earl B. Ray
H. Walden Retan
Abraham I. Rosenstein
Oscar F. Rosenow

Earl Saxe
Walter L. Schafer

Israel A. Schiller
Louis A. Schwartz
Solomon Silver
Elmer R. Smith
Saul L. Solomon

Gordon B. Tayloe
Kent H. Thayer
Morris C. Thomas
Arthur M. Tunick
Kilby P. Turrentine
Gilman R. Tyler

Wesley Van Camp

Richard Wagner
Levi M. Walker
Lorenz M. Waller
Bernard A. Watson
Fitz-John Weddell, Jr.
Lee Williamson
Willis D. Wright

In the News Notes section of the January, 1943, issue of this journal we reported the election of 147 Fellows and 140 Associates. With these additions and with other adjustments made in the College membership at the meeting of the Board of Regents, December 13, 1942, such as reinstatements and deletions due to the expirations of the maximum five-year Associate term, the total membership of the College now is as follows:

4	Masters
3,844	Fellows
1,118	Associates
4,966	

New Life Member

Dr. Charles Leonard Hess, F.A.C.P., Bay City, Mich., became a Life Member of the American College of Physicians on January 5, 1943.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Charles J. Bloom, F.A.C.P., New Orleans, La.—"The Care and Feeding of Babies in Warm Climates";
Dr. Henry A. Christian, F.A.C.P., Brookline, Mass.—"Osler's Principles and Practice of Medicine," 14th edition.

Reprints

Dr. Alvan L. Barach, F.A.C.P., New York, N. Y.—51 reprints;
Dr. Edward W. Cannady, F.A.C.P., East St. Louis, Ill.—1 reprint;
Dr. O. P. J. Falk, F.A.C.P., St. Louis, Mo.—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—2 reprints;
Jerome S. Levy (Associate), Captain, (MC), U. S. Army—2 reprints;
Horace P. Marvin, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—1 reprint;
Dr. Ralph M. Tandowsky, F.A.C.P., Los Angeles, Calif.—2 reprints.

The Reading Hospital, Reading, Pa., contributed a copy of the "History of the Reading Hospital, 1867–1942" to the College Library. This History was published by the Board of Managers of the Hospital on the occasion of its 75th anniversary, December 9, 1942.

Colonel Otis O. Benson, (MC), U. S. A. (Associate), is Chief of the Aero Medical Laboratory, Engineering Division, that has been recently built and equipped at the Army Air Forces Materiel Center, Wright Field, Dayton, Ohio.

"Physiology of Flight—Human Factors in the Operation of Military Aircraft" is the title of a book containing a compendium of lectures and demonstrations given to the Army Air Force personnel, and prepared by the Aero Medical Research Laboratory under Colonel Benson. Information is being simplified by illustrating it in the best "Popular Mechanics" manner, and will be published as a Technical Order for all flying personnel to read. Colonel Benson has contributed a copy of this publication to the College Library.

Manpower Commission and Medical Care for Civilians

Mr. Paul V. McNutt, Chairman of the War Manpower Commission, on January 10 made the announcement that every effort to furnish adequate medical care for civilians would be made. His statement was based on a report by Dr. Frank H. Lahey, Chairman of the Directing Board, Procurement and Assignment Service for Physicians, Dentists and Veterinarians.

Some physicians, Dr. Lahey indicated, will be asked to volunteer for practice in areas other than those in which they are now located. This will be done to assure at least a minimum standard of medical care. It is hoped that in most instances relocation of a physician can be accomplished within the States in which he is now licensed. To obtain greater mobility of physicians, it is pointed out that some method of temporary licensing for the duration will probably have to be arranged in some States. More than 400 physicians have already been relocated. The names of other physicians who are willing to be and who can be relocated are being submitted to the Procurement and Assignment Service. The U. S. Public Health Service and the Procurement and Assignment Service are making careful studies of industrial and other critical areas where relatively large numbers of physicians will be needed. In estimating the availability of physicians for civilian or military service, certain adjustments are made for (1) lessened effectiveness of those over 65; (2) number of physicians giving full time service in certain Governmental and private agencies; (3) numbers now acting as residents and house officers.

The total number of American physicians is approximately 180,000. It is estimated that the medical needs of the Armed Forces in 1943 can be met with an additional 10,000 physicians, and there will be left more than 80,000 active civilian physicians, estimated as sufficient to care for the needs of the civilian population if properly distributed and allocated, and if civilians will take every possible health precaution to keep well.

Recruiting in 1943 will be confined to States with a disproportionately large number of physicians. At the present time the following States show shortages of physicians: Alabama, Arizona, Arkansas, Colorado, Georgia, Idaho, Kentucky, Louisiana, Mississippi, New Mexico, North Carolina, South Carolina, South Dakota, Tennessee and West Virginia.

A. C. P. Postgraduate Courses

The 1943 Bulletin of Postgraduate Courses was distributed to all members of the College in late December. The Program for 1943 was greatly reduced, there being

only three courses, all in Internal Medicine: No. 1, University of Minnesota Center for Continuation Study, January 25–30; No. 2, The Mayo Foundation, University of Minnesota, and The Mayo Clinic, February 1–6; No. 3, Boston University School of Medicine, Massachusetts Memorial Hospitals, April 5–10.

Courses 1 and 2 were closely coördinated, with the result that most of the registrants took both courses. The registration for these two courses, now completed, exceeded all expectations of the Advisory Committee on Postgraduate Courses. Physicians were in attendance from all parts of the United States and Canada, and the signal success of these courses proved conclusively that such opportunities are definitely in demand during the War.

Course 3 at the Boston University School of Medicine, under the direction of Dr. Chester S. Keefer, F.A.C.P., April 5–10, also has a gratifying registration. There is still time to register, but the maximum number that can be accommodated is nearly reached.

The 5th Annual Congress on Industrial Health, sponsored by the Council on Industrial Health of the American Medical Association, was held in Chicago, Ill., January 11–13, 1943. Among those who participated in the program were:

Dr. John H. Foulger, F.A.C.P., Wilmington, Del.—"Preventive Medicine in Industry";

Dr. Chester S. Keefer, F.A.C.P., Boston, Mass.—"Respiratory Infections in Industry: Joint Report Prepared by the Council on Pharmacy and Chemistry and the Council on Industrial Health, American Medical Association";

Dr. James P. Leake, F.A.C.P., Bethesda, Md.—"Vaccines and Serums: Indications and Procedure";

Dr. Lemuel C. McGee, F.A.C.P., Wilmington, Del.—"Occupational Disease in Munitions Workers";

Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill.—"The Older Worker";

Dr. Raymond Hussey, F.A.C.P., Baltimore, Md.—"Report of the Committee on Workmen's Compensation of the Council on Industrial Health."

Thomas F. Duhigg, F.A.C.P., Commander, (MC), U. S. Navy, has been elected President of the Society of Ex-Resident and Resident Physicians of the Philadelphia General Hospital.

Dr. Andrew L. Banyai (Associate), Wauwatosa, Wis., spoke on "Non-tuberculous Pulmonary Infections" at a meeting of the West Allis Medical Society, West Allis, Wis., December 3, 1942.

Dr. John C. White, F.A.C.P., New Britain, Conn., has been appointed Superintendent of the New Britain General Hospital.

Arthur P. Hitchens, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army, was one of the speakers at the meeting of the Medical Society of the District of Columbia, November 18, 1942. This meeting was devoted to a panel discussion on "Undulant Fever, Brucellosis and Bang's Disease."

Dr. Francis E. Harrington, F.A.C.P., Minneapolis, Minn., was recently appointed Director of the Minneapolis General Hospital.

Lloyd R. Newhouser, F.A.C.P., Commander, (MC), U. S. Navy, spoke on "Treatment of Shock, Including Use of Blood Plasma" at the annual combined medical-dental meeting of the organized medical and dental professions of Greater New York, December 7, 1942.

Dr. Howard K. Petry, F.A.C.P., Harrisburg, Pa., spoke on "Shock Treatment of Psychoses" at a recent meeting of the Dauphin (Pa.) County Medical Society in Harrisburg.

The Medical Society of Milwaukee (Wis.) County sponsored a series of three lectures on the gastro-intestinal tract, November 2–4, 1942. Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., discussed "Functional Disorders"; Dr. J. Edwin Habbe, F.A.C.P., Milwaukee, discussed "Neoplasms"; and Dr. William M. Jermain, F.A.C.P., Milwaukee, discussed "Inflammatory Disorders."

The President of the United States has renominated Ross T. McIntire, F.A.C.P., Rear Admiral, (MC), U. S. Navy, to be Chief of the Bureau of Medicine and Surgery of the U. S. Navy. Admiral McIntire has been a member of the Medical Corps of the U. S. Navy since 1917 and was first appointed Surgeon General of the Navy in 1938.

Dr. Moses Barron, F.A.C.P., Minneapolis, Minn., spoke on the "Medical Management of Peptic Ulcer" at a meeting of the Minnesota Academy of Medicine in St. Paul, October 14, 1942.

Dr. Lloyd F. Craver, F.A.C.P., New York, N. Y., discussed "Cancer and Allied Disorders" at a meeting of the Dauphin (Pa.) County Medical Society in Harrisburg, December 1, 1942.

At the recent meeting of the American Public Health Association in St. Louis, Mo., Dr. Felix J. Underwood, F.A.C.P., Jackson, Miss., was named President-Elect.

On November 13, 1942, Philip S. Hench, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army, addressed the El Paso (Colo.) County Medical Society at Camp Carson Base Hospital. Colonel Hench spoke on "Management of Chronic Arthritis."

At a meeting of the Medical Society of the District of Columbia, December 9, 1942, commemorating its 125th anniversary, Dr. Arthur C. Christie, F.A.C.P., Washington, D. C., a Past President of the Society, spoke on "Medicine in the Nation's Capital, 1817–1942."

At a midwinter scientific session of the Central States Society of Industrial Medicine and Surgery held in Chicago, Ill., December 11, 1942, Dr. Italo F. Volini, F.A.C.P., Chicago, spoke on "Sulfon Drug Therapy."

Dr. Louis N. Katz, F.A.C.P., Chicago, Ill., spoke on "The Diagnostic Value of the Electrocardiogram Based on an Analysis of 149 Autopsied Cases," and Dr. George E. Wakerlin, F.A.C.P., Chicago, Ill., spoke on "Treatment of Experimental

Renal Hypertension" at a joint meeting of the Chicago Society of Internal Medicine and the Clinical Section of the Chicago Heart Association.

Students and members of the faculty at Cornell University, Ithaca, N. Y., recently coöperated in a two-week experiment to test new vaccines. The experiment was under the direction of the Army Influenza Commission and was directed by Dr. Norman Plummer, F.A.C.P., and Dr. Herbert K. Ensworth (Associate), both of New York, N. Y.

Dr. Charles E. Lyght, F.A.C.P., Professor of Health and Physical Education for Men and Director of the Carleton College Health Service, Northfield, Minn., has been appointed Director of Health Education of the National Tuberculosis Association.

Dr. Raymond Hussey, F.A.C.P., Baltimore, Md., has been named a member of the Medical Committee of the Industrial Hygiene Foundation.

Edward R. Stitt, F.A.C.P., Rear Admiral, Retired, (MC), U. S. Navy, was one of three military physicians who was presented with the first awards of the newly established Gorgas Medal. Admiral Stitt was cited "for extensive research and writing on tropical maladies and their prevention."

These awards were recently established by John Wyeth and Brother, Inc., Philadelphia, Pa., in memory of Surgeon General William Gorgas, whose work in preventive medicine made it possible to construct the Panama Canal. The awards include silver medals inscribed with the likeness of General Gorgas and a cash award of $500.00.

Dr. Israel M. Rabinowitch, F.A.C.P., Associate Professor of Medicine, McGill University Faculty of Medicine, Montreal, Quebec, conducted a course of lectures and demonstrations on "Chemical Warfare," October 19–30, 1942, sponsored by McGill University Faculty of Medicine under the auspices of the Director of Civil Air Raid Precautions.

At the annual meeting of the Institute of Medicine of Chicago, December 10, 1942, Dr. George H. Coleman, F.A.C.P., was named Secretary and Dr. Grant H. Laing, F.A.C.P., Treasurer.

On December 16, 1942, the Polk (Iowa) County Medical Society conducted a panel discussion on "The Sulfonamides." The discussion was under the direction of Dr. Daniel J. Glomset, F.A.C.P., Des Moines, Iowa.

Dr. Arthur F. Chace, F.A.C.P., New York, N. Y., was elected President of the New York Academy of Medicine, December 3, 1942, to serve for a two-year term. Dr. Cornelius P. Rhoads, F.A.C.P., New York, N. Y., was elected a Vice President of the Academy to serve for a three-year term.

At the 62nd Annual Dinner of the Associated Alumni of the College of the City of New York, November 14, 1942, Dr. Alvan L. Barach, F.A.C.P., New York, N. Y.,

was awarded one of the Townsend Harris Medals in recognition of "notable post-graduate attainments."

On March 10, 1943, Dr. Cornelius P. Rhoads, F.A.C.P., New York, N. Y., will address a special meeting of the College of Physicians of Philadelphia. Dr. Rhoads will speak on "Newer Advances in Cancer Research."

Dr. William E. Robertson, F.A.C.P., Philadelphia, Pa., was one of the physicians honored for having completed fifty years or more in the practice of medicine by the Philadelphia County Medical Society at a luncheon meeting, January 12, 1943.

At a meeting of the North Texas District Medical Association held in Dallas, Tex., November 30, 1942, Dr. Chester M. Jones, F.A.C.P., Boston, Mass., spoke on "Clinical Problems in Hepatic Disease" and Dr. James H. Means, F.A.C.P., Boston, Mass., on "Diseases Affecting the Portal Circulation."

On December 18, 1942, the University of Texas Medical Branch, Galveston, conducted a special war program at its semicentennial graduation exercises. Among the speakers were:

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.—"Blood and Substitutes in Shock";
Dr. Franklin G. Ebaugh, F.A.C.P., Denver, Colo.—"Psychiatry and War";
Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill.—"Obstacles in the Path of an Optimum Diet."

The 5th Annual Forum on Allergy was held in Cleveland, Ohio, January 9–10, 1943. Study groups were conducted by the following members of the College:

Dr. Theodore L. Squier, F.A.C.P., Milwaukee, Wis.—"Allergic Manifestations in the Blood";
Dr. John P. Henry, F.A.C.P., Memphis, Tenn.—"Allergic Headaches";
Dr. Herbert J. Rinkel, F.A.C.P., Kansas City, Mo.—"Food Allergy";
Dr. J. Warrick Thomas, F.A.C.P., Cleveland, Ohio—"Allergy of the Eye and Conjunctiva";
Dr. Karl D. Figley, F.A.C.P., Toledo, Ohio—"Vasomotor Rhinitis in Children";
Dr. Ralph Bowen, F.A.C.P., Houston, Tex.—"The Prevention of Allergy in Children";
Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill.—"Asthma in Patients Over Forty-Five Years of Age";
Dr. Homer E. Prince, F.A.C.P., Houston, Tex.—"Allergy to Fungi";
Dr. George L. Waldbott, F.A.C.P., Detroit, Mich.—"Industrial Allergic Dermatitis."

Dr. Milton B. Cohen, F.A.C.P., Cleveland, delivered a special lecture on "The Dynamic Mechanism of the Allergic Reaction" and Dr. Roy W. Scott, F.A.C.P., Cleveland, on "Cardiac Asthma and the Heart in Asthma."

Dr. Elmer E. Glenn, F.A.C.P., Springfield, Mo., was recently named President of the Missouri Tuberculosis Association.

Dr. Charles H. Neilson, F.A.C.P., St. Louis, Mo., has been chosen Vice President of the Missouri State Board of Health.

A series of lectures on legal medicine are being conducted Friday evenings by the Office of the Coroner of Philadelphia (Pa.) County, January 8–March 12, 1943. Among the local speakers were:

January 8, 1943—Dr. Edward B. Krumbhaar, F.A.C.P.—"Causes of Sudden Death";
January 29, 1943—Dr. Edward A. Strecher, F.A.C.P.—"Suicide."

At a meeting of the Allegheny (Pa.) County Medical Society in Pittsburgh, December 15, 1942, Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, spoke on "Management of Diabetic Emergencies" and Dr. Angelo L. Luchi (Associate), Wilkes-Barre, on "Diabetic Diets and Food Habits of the Nationalities."

Dr. Chester N. Frazier, F.A.C.P., has been appointed Professor of Dermatology and Syphilology at the University of Texas Medical Branch in Galveston. Dr. Frazier was recently engaged in venereal disease control work at the Johns Hopkins School of Hygiene and Public Health, Baltimore, Md.

Dr. Frank Krusen, F.A.C.P., Rochester, Minn., officially represented the American College of Physicians recently when the Army-Navy "E" Production Award was made to H. G. Fisher & Co., Chicago. Dr. John S. Coulter represented the American Medical Association, Dr. Bowman C. Crowell, the American College of Surgeons and Dr. W. P. Morrell, the American Hospital Association. The Governor of the State of Illinois was represented by Major General Frank Parker, formerly Commander of the First Division in France, who made an address. Honorable Edward J. Kelly, Mayor of the City of Chicago, also made an address. The Award was made by Rear Admiral K. C. Melhorn (MC), U. S. N. (F.A.C.P.), and the pins were awarded by Lieutenant Colonel M. E. Griffin, (MC), U. S. A. The Navy provided a color guard and a twenty-eight piece band. The ceremony was inspiring and was attended by many men of prominence.

The Medical and Surgical Relief Committee of America reports receipt of seventy-six cartons containing about five thousand pounds of surgical instruments rescued from scrap metal collections. They were donated by Dr. Walter L. Bierring, F.A.C.P., State Health Commissioner of Iowa, when it was learned that many of the instruments contributed to the recent Iowa scrap metal campaign were in good condition and would more effectively serve the war effort if reconditioned and made available to the various organizations which call on the Committee for help. After necessary repairs have been made, the instruments will be placed in emergency medical field sets for distribution to the U. S. Coast Guard, and to first aid posts, needy hospitals and other recognized relief agencies in the United States and Alaska.

SPECIAL NOTICES

Announcement

The American Board of Internal Medicine

Pursuant to the policy of the American Board of Internal Medicine to keep fees at a minimum consistent with efficient function of the Board, it is now possible to

reduce the registration and examination fee. Accordingly, the following action has been directed: The registration and examination fee will be reduced from forty dollars to thirty dollars. The certificate fee will remain at ten dollars, making a total of forty dollars. The oral examination fee in the sub-specialties will remain at ten dollars.

This reduction in fees will become effective as of January 1, 1943, and will apply to candidates for the written examination on February 15, 1943 whose applications have not been accepted for a previous examination.

ERNEST E. IRONS, M.D.,
Chairman

CLEVELAND HEALTH MUSEUM

On the eve of its second anniversary civic luncheon November 20, 1942, Cleveland Health Museum received its first truck loads of exhibit material presented for the duration by the American Museum of Health, New York City. These accessions were selected from the Oberlaender Trust Collection and others displayed in the Hall of Man and Medicine at the New York World's Fair.

The exhibits chosen include such famous pieces as the muscle man, the nerve man, a body book of 16 pages, the nodding head, swinging ear, and acting heart. Models of cell development demonstrate marvels of heredity. More than 300 exhibit items show what is needed to keep the body running, what hazards threaten its existence, and what limitations must be considered affecting its use.

Most widely known is the Transparent Man whose outer form is modeled after the fourth century Greek statue of "The Praying Boy" which was once in the possession of Frederick the Great of Prussia. This exhibit, symbolic of the others which will be given special showings at the Museum in the beginning of 1943, was unveiled by Mrs. Elizabeth S. Prentiss whose support has helped immeasurably to sustain the Museum.

W. W. Peter, M.D., Dr. P. H., associate professor of public health, Yale University, spoke on "Keep the Health Fires Burning." He told how poor health is reducing manpower in this country. One out of five people in the productive age group (20 to 64 years old) are handicapped by chronic diseases, serious mental or physical illness. "Every state and city has its share of these unproductive people," Dr. Peter said. It is important to mention them because "your Museum here and all other contributing agencies can do something to improve conditions."

Bruno Gebhard, M.D., director of Cleveland Health Museum, who has been instrumental in the designing of New York World's Fair's health exhibits, came to Cleveland in 1940, to design and install exhibit material for its opening and to operate the Museum.

Since its opening, November 13, 1940, it has been visited by more than 66,000 people.

But its influence has been far more widespread than these statements indicate. The attendance figures include people who came from 44 states and several foreign countries, to take the message of Cleveland Health Museum back with them. By means of travelling exhibits the Museum has gone far beyond the territorial limits. It is estimated that more than a half million people from Boston and Bridgeport, to Huron, South Dakota and Huston, Texas, have seen the Museum's dramatic presentations of health facts.

OBITUARIES

DR. SHERMAN GRANT BONNEY

Following a brief illness, Sherman Grant Bonney, F.A.C.P., died in Denver on November 19, 1942. Dr. Bonney was born in Cornish, Maine, in 1864, the son of Dr. and Mrs. Calvin Fairbanks Bonney. In 1886, he received his A.B. degree at Bates College, Lewiston, Maine; in 1889, he received his M.A. degree from the same institution. In 1889, he received the degree of M.D. from Harvard Medical School.

After practicing for a brief period of time in Lewiston, Maine, where he married Miss Nancy B. Little, he came to Denver in 1890, and was in the active practice of medicine in this city until he retired in 1930.

During the course of a very long and active professional life, Dr. Bonney was Professor of Medicine and Dean of the Medical Department at Denver University, and Trustee and President of the Gross Medical College of Denver. At the time of the amalgamation of Colorado medical institutions, about 1910, Dr. Bonney was made Professor of Medicine, Emeritus, of the University of Colorado School of Medicine.

In 1908, he married Mrs. Jessie Ellwood Ray who survives him. In 1908, he published a textbook on tuberculosis, "Pulmonary Tuberculosis and Its Complications." This book, a pioneer in its field, embodied the experience of an enormous practice in tuberculosis, and brilliantly recorded the observations of a very keen mind. The second edition of this work appeared in 1910. In memory of his parents, he presented a public library to Cornish, Maine.

He was a member of the Medical Society of the City and County of Denver, the Colorado State Medical Society, the Denver Clinical and Pathological Society, a Fellow of the American College of Physicians, a Fellow of the American Medical Association, a member of the American Clinical and Climatological Association, the National Tuberculosis Association and the American Society for Tropical Medicine.

During the period of great popularity of Colorado as a health resort for tuberculous patients, Dr. Bonney enjoyed a great reputation. His practice at this time was enormous. He combined great diagnostic skill with a native shrewdness of judgment of human nature and a dogged determination to get his patient well. His retirement in 1930 was due solely to a failure of hearing. His health remained good up to the past year. His mental faculties, always very keen, were unimpaired up to the last.

JAMES J. WARING, M.D., F.A.C.P.,
Governor for Colorado

DR. FREDERICK FRETAGEOT GUNDRUM

Dr. Frederick Fretageot Gundrum of Sacramento, California, one of our prominent physicians of northern California and a Fellow of the American College of Physicians since 1919, died on October 23, 1942.

Dr. Gundrum was born at New Harmony, Indiana, November 3, 1880. He graduated from the academic department of Stanford University in 1903 and from the Johns Hopkins University School of Medicine in 1908. He served an internship at the Johns Hopkins Hospital 1908 to 1909 and a residency at the St. Francis Hospital, Pittsburgh, Pennsylvania, from 1909 to 1910. He was also Demonstrator in Anatomy at the Pittsburgh School of Medicine from 1909 to 1910. From 1912 to 1915 he was Director of the Northern Branch of the California State Hygienic Laboratory, and later Vice-President of the California State Board of Health, serving for several years. He served as a Member of the Staff of the Sacramento County Hospital for several years and was also Secretary and Member of the Board of Directors of Sutter Hospital, in Sacramento. In 1937 he was President of the San Francisco Academy of Medicine. He was a member of the California State Medical Society, Fellow of the American Medical Association, member of the American Public Health Association, and Diplomate of the American Board of Internal Medicine. He was the author of many published papers and for many years was a regular attendant and active participant in the annual meetings of the California State Medical Society.

Dr. Gundrum was long a prominent physician in California and wielded an important influence in his community. His work in the Public Health field, which was an ancillary interest, was an important contribution to the State of California as he was one of the pioneers in this field and possessed the vision and administrative ability necessary for constructive effort.

He married Elizabeth Adams, September 3, 1913. She and two children, Elizabeth Eloise, and Frederick, Junior, survive.

ERNEST H. FALCONER, M.D., F.A.C.P.,
Governor for Northern California

DR. HORTON RYAN CASPARIS

Horton Ryan Casparis, F.A.C.P., of Nashville, Tennessee, died November 11, 1942, in Richmond, Virginia, where he was attending a Meeting of the Southern Medical Association.

He was born at Round Mountain, Texas, in 1891. He graduated from the University of Texas in 1915 and received his degree in Medicine at the Johns Hopkins University in 1919. He served his internship at the Willard Parker Hospital in New York City. Later, he became staff assistant at the Trudeau Sanatorium and then returned to Johns Hopkins for postgraduate work where he remained until 1924. The next year he spent his time visiting various European Clinics.

Dr. Casparis joined the Faculty of the Vanderbilt University School of Medicine in 1925 and became Professor of Pediatrics there in 1928.

He was Chairman of the Section on Pediatrics of the American Medical Association and the Southern Medical Association; Pediatrician-in-Chief, Vanderbilt University Hospital since 1925; former President, Tennessee Tuberculosis Association; Diplomate, American Board of Pediatrics; formerly, Chairman of the Advisory Committee on Maternal and Child Health Services of the U. S. Children's Bureau; President of the Southern Trudeau Society; President of the American Board of Pediatrics; Member of the Editorial Board of the American Journal of Diseases of Children; author of numerous published articles on tuberculosis in children, allergy and the various aspects of the mental health problems in children; member of the Davidson County Medical Society, the Tennessee State Medical Association, the American Pediatric Society, the American Academy of Pediatrics, National Tuberculosis Association, and Fellow of the American College of Physicians since 1929.

Dr. Casparis made friends easily and was greatly admired by both the members of the Vanderbilt faculty and the student body.

Nashville, the State of Tennessee and the entire Nation have lost an invaluable, skillful worker who gave most of his time in improving methods of treatment and general knowledge pertaining to the two subjects he seemed most interested in: Tuberculosis and child mental health.

WILLIAM CALVERT CHANEY, M.D., F.A.C.P.,
Governor for Tennessee

DR. MAURICE L. RIPPS

Dr. Maurice L. Ripps, F.A.C.P., who had practiced Pediatrics in Elizabeth, N. J., for the past fifteen years, died on October 28, 1942, at the Elizabeth General Hospital following a brain operation.

Dr. Ripps was highly esteemed by his Associates, and the Clinical Society and Staff of the Elizabeth General Hospital have raised several hundred dollars to place needed equipment in the Children's Ward of the hospital as a memorial. He had been Assistant Attending in Pediatrics at this hospital for twelve years, having been very actively interested in that specialty from the time of his graduation in medicine.

Dr. Ripps was born in Bayonne, N. J., December 11, 1899. He received his B.S. degree, 1922 and his M.D. degree, 1923 from the University of Michigan. The ensuing four years he spent in preparing himself thoroughly in Pediatrics. His first interneship was for eighteen months at the Jersey City Hospital, and his second at the Willard Parker Hospital, New York. Residencies followed at the Stamford General Hospital, the Children's Hospital in Detroit and the University Hospital at Ann Arbor, Mich.

During an interim between two of these appointments, he served as Clinical Assistant at the New York Post-Graduate Medical School.

In 1927 he took up the practice of Pediatrics in Elizabeth, N. J., where he worked until his death. During his first three years of practice, he served as Clinical Instructor at Bellevue Hospital Medical College, New York City. He soon became too much occupied with his increasing responsibilities in Elizabeth to continue the work in New York. He was made Assistant Attending in Pediatrics at the Elizabeth General Hospital in 1930, and the following year received a similar appointment at the St. Elizabeth Hospital, both of which positions he occupied at the time of his death. He was Pediatrician to St. Walpurga's Orphanage, Roselle, N. J., to the Seaview Tubercular Hospital on Staten Island, and, since 1938, consulting Pediatrician to Alexian Brothers Hospital, Elizabeth, N. J.

Dr. Ripps was a member of the St. Elizabeth Clinical Society, the Elizabeth General Clinical Society, the Union County Medical Society, the Medical Society of New Jersey and the American Academy of Pediatrics. He was a Diplomate of the American Board of Pediatrics, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1934.

Dr. Ripps's untimely death at the age of forty-three leaves a large gap in the medical circles to which he belonged. He is survived by his wife and a son.

GEORGE H. LATHROPE, M.D., F.A.C.P.,
Governor for New Jersey

DR. HUBERT WORK

Dr. Hubert Work, F.A.C.P., former United States Postmaster General and Secretary of the Interior, died in Denver, December 14, 1942, at the age of eighty-two.

Dr. Work was born in 1860 on a farm in Indiana County, Pennsylvania. He worked his way through the Indiana State (Pa.) Normal School, matriculated in 1882 at the Medical Department of the University of Michigan, which he left after two years, and graduated in 1885 as a Doctor of Medicine from the University of Pennsylvania.

In 1888, he came West, practiced medicine at Greeley and Fort Morgan, Colorado, and later settled at Pueblo, where he founded the Woodcroft Hospital for mental diseases.

He was a Past-President of the Colorado State Medical Society and the American Psychiatric Association. He was President of the American Medical Association in 1921 and a Fellow of the American College of Physicians since 1921.

Always a staunch Republican, Hubert Work became one of the leaders of his party in Colorado, progressing from national committee-man for his

state to the United States Cabinet and Chairmanship of the National Republican Committee. These important responsibilities took him out of the active practice of his profession, but his faithful attendance at many medical meetings and his loyal devotion to his medical colleagues attested to his never-failing interest in the welfare of the medical profession. His friends, lay and professional, were innumerable. It can be said that he achieved great success in his profession, in business and in the political field.

JAMES J. WARING, M.D., F.A.C.P.,
Governor for Colorado